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(54) Title: PROPENAMIDES AS CCR5 MODULATORS

(57) Abstract

This invention relates to substituted anilides which are modulators, agonists or antagonists, of the CCR5 receptor. In addition, this invention relates to the treatment and prevention of disease states mediated by CCR5.

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PROPENAMIDES AS CCR5 MODULATORS

FIELD OF THE INVENTION

This invention relates to substituted anilides which are modulators, agonists or antagonists, of the CC chemokine receptor CC-CKR5 now designated as CCR5 (Nature Medicine, 2: 1174-8, 1996). In addition, this invention relates to the treatment and prevention of disease states mediated by CCR5.

BACKGROUND OF THE INVENTION

T cells are not only key regulators of the immune response to infectious agents but are believed critical for the initiation and maintenance of the inflammatory reaction in a variety of chronic diseases. Increased numbers or enhanced activation state of T cells, especially CD4+ T cells, have been demonstrated in the synovium of individuals with rheumatoid arthritis (M.J. Elliott and R. N. Maini, Int. Arch. Allergy Immunol. 104: 112-1125, 1994), in the bronchial mucosa of asthmatics (C.J. Corrigan and A.B. Kay, Immunol. Today 13: 501-506, 1992), in the lesions of multiple sclerosis (R. Martin and H. F. McFarland, Crit. Rev. Clin. Lab. Sci. 32: 121-182, 1995), in psoriatic lesions (J.L. Jones, J. Berth-Jone, A. Fletcher and P.E. Hutchinson, J. Pathol. 174: 77-82, 1994) and in the fatty streaks of atherosclerosis (R. Ross, Annu. Rev. Physiol. 57: 791-804, 1995).

T cells, as well as other inflammatory cells, will migrate into tissues in response to the production of a variety of chemotactic factors. Among these factors are a superfamily of 8-12 kDa proteins known as the chemokines. These proteins share structural features such as the presence of 3-4 conserved cysteine residues. RANTES, which stands for Regulated upon Activation Normal T cell Expressed and Secreted, is a 8 kDa protein member of CC branch of the chemokine family. These proteins recruit and activate immune and inflammatory cells through an interaction with G-protein coupled receptors. The CC branch is defined by the absence of an intervening amino acid residue between the first two cysteine residues and members of this family predominately elicit the migration of mononuclear cells, eosinophils and basophils (M. Baggiolini, B. Dewald, and B. Moser, Adv. Immunol. 55: 97-179, 1994; and J.J. Oppenheim, C.O.C. Zachariae, N. Mukaida, and K. Matsushima, Annu. Rev. Immunol. 9: 617-648, 1991).

RANTES potently produces chemotaxis of T cells, basophils, eosinophils, monocytes and mast cells. RANTES was originally identified as gene product induced late after antigen activation of T-cells (T.J. Schall, J. Jongstra, B.J. Dyer, J.

Jorgensen, et al., J. Immunol. 141:1018-1025, 1988), however, RANTES has been shown to be synthesized and secreted by a diverse group of cells that include epithelial and endothelial cells (C. Stellato, L.A. Beck, G.A. Gorgone, D. Proud, et al., J. Immunol. 155: 410-418, 1995; and A. Marfaing-Koka, O. Devergne, G. Gorgone, A. Portier, et al., J. Immunol. 154: 1870-1878, 1994), synovial fibroblasts (P. Rathanaswami, M. Hachicha, M. Sadick, T.J. Schall, et al., J. Biol. Chem. 268: 5834-5839, 1993) and dermal fibroblasts (M. Sticherling, M. Kupper, F. Koltrowitz, E. Bornscheuer, et al., J. Invest. Dermatol. 105: 585-591, 1995), mesangial cells (G. Wolf, S. Aberle, F. Thaiss, et al., Kidney Int. 44: 795-804, 1994) and platelets (Y. Koameyoshi, A. Dorschner, A.I. Mallet, E. Christophers, et al., J. Exp. Med. 176: 587-592, 1992). In these cells, RANTES mRNA is rapidly upregulated in response to IL-1 or TNFα. Although RANTES mRNA is not usually detected in normal tissues (J.M. Pattison, P.J. Nelson, and A.M. Krensky, Clin. Immunother. 4: 1-8, 1995), increased mRNA or protein has been found in diseases characterized by a mononuclear infiltrate. For example, RANTES mRNA was visualized using *in situ* hybridization in renal allografts undergoing rejection (J.M. Pattison, P.J. Nelson, and A.M. Krensky, Clin. Immunother. 4: 1-8, 1995; and K.C. Nadeau, H. Azuma and N.I. Tilney, Proc. Natl. Acad. USA 92: 8729-8733, 1995) in the skin of atopic dermatitis patients after exposure to antigen (S. Ying, L. Taborda-Barata, Q. Meng, M. Humbert, et al., J. Exp. Med. 181: 2153-2159, 1995), and in endothelial cells of coronary arteries undergoing accelerated atherosclerosis after cardiac transplant (J.M. Pattison, P.J. Nelson, and A.M. Krensky, Clin. Immunother. 4: 1-8, 1995). Further, increased immunoreactive protein for RANTES has been detected in bronchoalveolar lavage fluid (R. Alam, J. York, M. Boyers, et al., Am. J. Resp. Crit. Care Med. 149: A951, 1994) and sputum from asthmatic individuals (C.M. Gelder, P.S. Thomas, D.H. Yates, I.M. Adcock, et al., Thorax 50: 1033-1037, 1995).

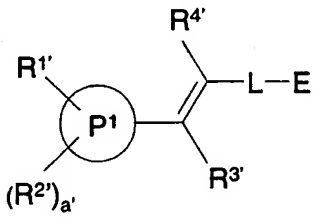
Several receptors have been identified that bind RANTES. In particular, CCR5, when expressed in either HEK 293 cells or CHO cells, binds RANTES. This receptor is expressed in T-cells and in monocytes and macrophages, immune/inflammatory cells which are important in the maintenance of a chronic inflammatory reaction. Pharmacological characterization of CCR5 indicates similarities to the RANTES binding site observed on isolated T cells. Therefore, antagonism of RANTES' action on CCR5, as well as antagonism of other natural modulators of CCR5, should inhibit the recruitment and activation of T cells and macrophages into inflammatory lesions and provide a novel therapeutic approach for the treatment of atopic and autoimmune disorders.

Since T cells express CCR5, selective receptor modulators of CCR5, particularly antagonists, are likely to provide beneficial effects in diseases including, but not limited to, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, atherosclerosis, sarcoidosis and other fibrotic disease, psoriasis, autoimmune diseases such as multiple sclerosis, and inflammatory bowel disease, all in mammals, preferably humans. Furthermore, since CD8+ T cells have been implicated in chronic obstructive pulmonary disorders (COPD), CCR5 may play a role in their recruitment and therefore antagonists to CCR5 could provide potential therapeutic in the treatment of COPD. Also since CCR5 is a co-receptor for the entry of HIV into cells, selective receptor modulators may be useful in the treatment of HIV infection.

Surprisingly, it has now been discovered that a class of non-peptide compounds, in particular substituted anilides of formula (I), function as CCR5 receptor modulators, and therefore, have utility in the treatment and prevention of disease states mediated by CCR5 receptor mechanisms.

SUMMARY OF THE INVENTION

In one aspect, the present invention is to novel compounds of formula (I), or pharmaceutically active salts thereof, and their novel use in treating the above-mentioned CCR5-mediated disease states:



(I)

wherein:

the basic nitrogen in moiety E may be optionally quaternized with C_{1-6}alkyl or is optionally present as the N-oxide;

P^1 is phenyl, fused bicyclic aryl, a 5- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulfur, or a fused bicyclic heterocyclic ring of 8 to 11 members containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulfur;

L is $CONR^{5'}$;

$R^{1'}$ and $R^{2'}$ are independently hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{3-6}cycloalkenyl, $(CH_2)_b NR^{6'}R^{7'}$, $(CH_2)_b NR^{6'}COR^{8'}$, $(CH_2)_b NR^{6'}CO_2R^{9'}$, $(CH_2)_b NR^{6'}SO_2R^{10'}$,

$(CH_2)_b$CONR$^{11'}$R$^{12'}$, hydroxyC_{1-6}alkyl, C_{1-4}alkoxyalkyl (optionally substituted by a C_{1-4}alkoxy or hydroxy group), $(CH_2)_b$CO$_2$$C_{1-6}$alkyl, $(CH_2)_c$OC(O)R$^{13'}$, CR$^{14'}$=NOR$^{15'}$, CNR$^{16'}$=NOR$^{15'}$, COR$^{17'}$, CONR$^{11'}$R$^{12'}$, CONR$^{11'}$$(CH_2)_dOC_{1-4}$alkyl, CONR$^{11'}$$(CH_2)_bCO_2R^{18'}$, CONHNR$^{19'}R^{20'}$, CONR$^{11'}SO_2R^{21'}$, CO$_2R^{22'}$, cyano, trifluoromethyl, NR$^{6'}$R$^{7'}$, NR$^{6'}$COR$^{8'}$, NR$^{23'}$CO$(CH_2)_b$NR$^{23'}$R$^{24'}$, NR$^{23'}$CONR$^{23'}$R$^{24'}$, NR$^{6'}$CO$_2$R$^{9'}$, NR$^{6'}$SO$_2$R$^{10'}$, N=CNR$^{23'}$NR$^{23'}$R$^{24'}$, nitro, hydroxy, C_{1-6}alkoxy, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, OC(O)NR$^{25'}$R$^{26'}$, SR$^{27'}$, SOR$^{28'}$, SO$_2$R$^{28'}$, SO$_2$NR$^{29'}$R$^{30'}$, halogen, C_{1-6}alkanoyl, CO$_2$$(CH_2)_bOR^{31'}$, or R$^{1'}$ is phenyl or R$^{1'}$ is a 5 to 7-membered heterocyclic ring containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulfur, which are optionally substituted by one or two of R$^{32'}$;

or R$^{1'}$ is an optionally substituted, fused carbocyclic ring of 5 to 7-members, which may be partly or wholly unsaturated, or R$^{1'}$ is an optionally substituted, fused heterocyclic ring of 5 to 7-members containing 1 to 4 heteroatoms selected from nitrogen, oxygen, or sulfur, which may be partly or wholly unsaturated;

R$^{3'}$ is hydrogen or C_{1-6}alkyl;

R$^{4'}$ is hydrogen, C_{1-6}alkyl, C_{1-6}alkylCONH, or halogen;

R$^{5'}$ is hydrogen or C_{1-6}alkyl;

R$^{14'}$, R$^{15'}$, R$^{16'}$R$^{17'}$, R$^{18'}$, R$^{19'}$R$^{20'}$, R$^{23'}$, R$^{24'}$, R$^{27'}$, and R$^{31'}$ are independently hydrogen or C_{1-6}alkyl;

R$^{6'}$ and R$^{7'}$ are independently hydrogen or C_{1-6}alkyl, or R$^{6'}$ and R$^{7'}$ together with the nitrogen to which they are attached, forms a 5- to 6-membered heterocyclic ring, which may optionally be substituted by an oxo group, and, when there are six members, may optionally contain in the ring one oxygen or one sulfur atom;

R$^{8'}$ is hydrogen, C_{1-6}alkyl, or C_{1-4}alkoxyalkyl;

R$^{9'}$, R$^{21'}$, and R$^{28'}$ are independently C_{1-6}alkyl;

R$^{10'}$ is C_{1-6}alkyl or phenyl;

R$^{11'}$ and R$^{12'}$ are independently hydrogen or C_{1-6}alkyl, or R$^{11'}$ and R$^{12'}$ together with the nitrogen to which they are attached form a 5- to 6-membered saturated heterocyclic ring which, when there are 6 ring members, may optionally contain in the ring one oxygen or one sulfur atom;

R$^{13'}$ is C_{1-4}alkyl, optionally substituted by a C_{1-6}alkoxy;

$R^{22'}$ is hydrogen or C_{1-6}alkyl optionally substituted with one or two substituents selected from C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, or $NR^{6'}R^{7'}$;

$R^{25'}$ and $R^{26'}$ are independently hydrogen or C_{1-6}alkyl, or $R^{25'}$ and $R^{26'}$ together with the nitrogen to which they are attached form a 5- to 6-membered heterocyclic ring which, when there are six ring members, may optionally contain in the ring one oxygen or sulfur atom;

$R^{29'}$ and $R^{30'}$ are independently hydrogen or C_{1-6}alkyl, or $R^{29'}$ and $R^{30'}$ together with the nitrogen to which they are attached form 5- to 6-membered heterocyclic ring which, when there are six ring members, may optionally contain in the ring one oxygen or one sulfur atom;

$R^{32'}$ is hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylOC_{1-6}alkyl, $CONR^{33'}R^{34'}$, $CO_2R^{35'}$, cyano, aryl, trifluoromethyl, $NR^{36'}R^{37'}$, nitro, hydroxy, C_{1-6}alkoxy, C_{1-6}alkanoyl, acyloxy, or halogen;

$R^{33'}$, $R^{34'}$, $R^{35'}$, $R^{36'}$, and $R^{37'}$ are independently hydrogen or C_{1-6}alkyl;

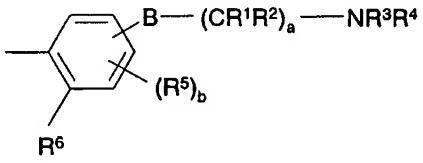
a' is 1, 2, or 3;

b' is 1, 2, 3 or 4;

c' is 0, 1, 2 or 3;

d' is 1, 2 or 3;

E represents (a):



(a);

in which

B is oxygen, $S(O)_c$, $CR^7{=}CR^8$, or CR^7R^8, or B is NR^9;

R^1 and R^2 are independently hydrogen or C_{1-6}alkyl; alternatively $B(CR^1R^2)_a$ is $OCR^1R^2CR^1(OH)CR^1R^2$ or $OCR^1R^2CR^1(OCOCH_3)CR^1R^2$;

R^3 and R^4 are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include C_{1-6}alkyl, aryl, $CONR^{10}R^{11}$, $NR^{10}R^{11}$, hydroxy, $OCOR^{12}$, $NHCOC_{0-6}$alkyl where alkyl is optionally substituted by OH, $NHCOCF_3$, $NHSO_2R^{13}$, and $NHCO_2R^{14}$;

R^5 is hydrogen, C_{1-6}alkyl, aryl, CN, $CONR^{15}R^{16}$, CO_2R^{17}, trifluoromethyl, $NHCO_2R^{18}$, hydroxy, C_{1-6}alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, OCF_3, $S(O)_dR^{19}$, $SO_2NR^{20}R^{21}$ or halogen;

R^6 is hydrogen, C_{1-6}alkyl, aryl, trifluoromethyl, hydroxy, C_{1-6}alkoxy or halogen, or R^6 taken together with $R^{5'}$ forms a group D where D is $(CR^{22}R^{23})_e$ or D is $(CR^{22}R^{23})_f$-G where G is oxygen, sulfur or $CR^{22}=CR^{23}$, $CR^{22}=N$, $=CR^{22}O$, $=CR^{22}S$, or $=CR^{22}-NR^{23}$;

R^7, R^8, R^{10}, R^{11}, R^{12}, R^{15}, R^{16}, R^{17}, R^{20}, R^{21}, R^{22}, and R^{23} are independently hydrogen or C_{1-6}alkyl;

R^9 is hydrogen, C_{1-6}alkyl, or phenylC_{1-6}alkyl;

R^{13}, R^{14}, R^{18}, and R^{19} are independently C_{1-6}alkyl;

a is 1, 2, 3, or 4;

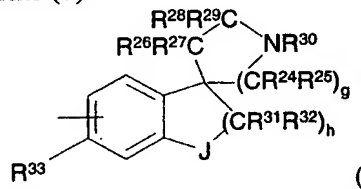
b is 1 or 2;

c and d are independently 0, 1 or 2;

e is 2, 3 or 4;

f is 0, 1, 2 or 3;

alternatively, E represents (b):



(b);

R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{31}, and R^{32} are independently hydrogen or C_{1-6}alkyl;

R^{30} is hydrogen, C_{1-6}alkyl, or C_{3-7}cycloalkyl;

R^{33} is hydrogen, C_{1-6}alkyl, trifluoromethyl, hydroxy or halogen, or R^{33} and $R^{5'}$ together form a group -K- where K is $(CR^{34}R^{35})_i$ or K is $(CR^{34}R^{35})_j$ -M and M is oxygen, sulfur, $CR^{34}=CR^{35}$, $CR^{34}=N$, or N=N;

J is oxygen, $CR^{36}R^{37}$, or NR^{38}, or J is a group $S(O)_k$;

R^{34}, R^{35}, R^{36}, R^{37}, and R^{38} are independently hydrogen or C_{1-6}alkyl;

g is 1, 2 or 3;

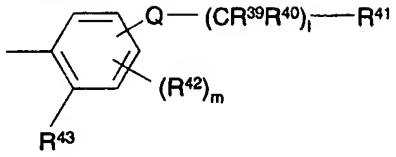
h is 1, 2 or 3;

i is 2, 3, or 4;

j is 0, 1, 2, or 3;

k is 0, 1 or 2;

alternatively, E represents (c):



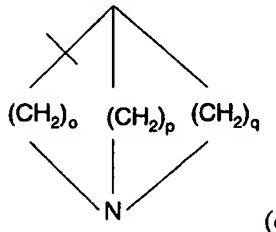
(c);

in which:

Q is oxygen, $S(O)_n$, $CR^{44}=CR^{45}$, $CR^{44}R^{45}$, or Q is NR^{46};

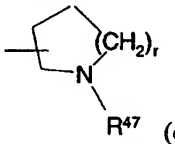
R^{39} and R^{40} are independently hydrogen or C_{1-6}alkyl;

R^{41} is a group of formula (d):



(d)

or R^{41} is a group of formula (e):



(e)

R^{42} is hydrogen, C_{1-6}alkyl, aryl, CN, $CONR^{48}R^{49}$, CO_2R^{50}, trifluoromethyl, $NHCO_2R^{51}$, hydroxy, C_{1-6}alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, OCF_3, $S(O)_sR^{52}$, $SO_2NR^{53}R^{54}$, or halogen;

R^{43} is hydrogen or R^{43} together with $R^{5'}$ forms a group R where R is $CR^{55}=CR^{56}$, $CR^{55}=CR^{56}CR^{55}R^{56}$, or $(CR^{55}R^{56})_t$;

R^{44}, R^{45}, R^{46}, R^{48}, R^{49}, R^{50}, R^{53}, R^{54}, R^{55}, and R^{56} are independently hydrogen or C_{1-6}alkyl;

R^{47} is hydrogen, C_{1-6}alkyl, or C_{3-7} cycloalkyl;

R^{51} and R^{52} are independently C_{1-6}alkyl;

l is 0, 1, 2, or 3;

m is 1 or 2;

n is 0, 1, or 2

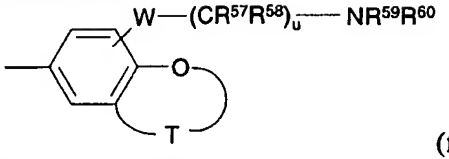
o, p, and q are independently integers having the value 1, 2, or 3;

r is 0,1, 2, or 3;

s is 0, 1, or 2;

t is 2 or 3;

alternatively, E represents (f):



(f);

R^{57} and R^{58} are independently hydrogen or C_{1-6}alkyl;

R^{59} and R^{60} are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include C_{1-6}alkyl, aryl, $CONR^{61}R^{62}$, $NR^{61}R^{62}$, hydroxy, $OCOR^{63}$, $NHCOC_{0-6}$alkyl where alkyl is optionally substituted by OH, $NHCOCF_3$, $NHSO_2R^{64}$, and $NHCO_2R^{65}$;

T is $-(CR^{66}R^{67})_v-$ or $-O(CR^{66}R^{67})_w-$;

W is oxygen, $S(O)_x$, NR^{68}, or W is $CR^{69}=CR^{70}$ or $CR^{69}R^{70}$;

R^{61}, R^{62}, R^{63}, R^{66}, R^{67} R^{68}, R^{69}, and R^{70} are independently hydrogen or C_{1-6}alkyl;

R^{64} and R^{65} are independently C_{1-6}alkyl;

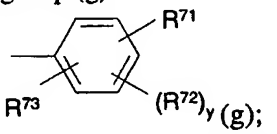
u is 1 to 4;

v is 2 or 3;

w is 1, 2, or 3;

x is 0, 1 or 2;

alternatively, E represents a group (g):



(g);

R^{71} is an optionally substituted 5 to 7-membered saturated or partially saturated heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, oxygen or sulfur or R^{71} is an optionally substituted 6,6 or 6,5 bicyclic ring containing a nitrogen atom and optionally a further heteroatom selected from oxygen, nitrogen or sulfur;

R^{72} is hydrogen, C_{1-6}alkyl, aryl, CN, $CONR^{74}R^{75}$, CO_2R^{76}, trifluoromethyl, $NHCO_2R^{77}$, hydroxy, C_{1-6}alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, OCF_3, $S(O)_zR^{78}$, $SO_2NR^{79}R^{80}$, or halogen;

R^{73} is hydrogen, C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy or halogen, or R^{73} and $R^{5'}$ taken together from a group -X- where X is $(CR^{81}R^{82})_{aa}$ or X is $(CR^{81}R^{82})_{ab}$-Y and Y is oxygen, sulfur or $CR^{81}=CR^{82}$;

R^{74}, R^{75}, R^{76}, R^{79}, R^{80}, R^{81}, and R^{82} are independently hydrogen or C_{1-6}alkyl;

R^{77} and $R^{78}$are independently C_{1-6}alkyl;

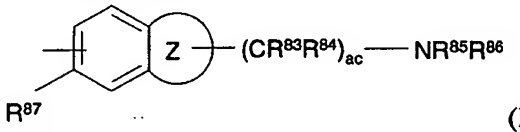
y is 1 or 2;

z is 0, 1, or 2;

aa is 2, 3 or 4;

ab is 0, 1, 2 or 3;

alternatively, E represents group (h):



(h);

R^{83} and R^{84} are independently hydrogen or C_{1-6}alkyl;

R^{85} and R^{86} are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include C_{1-6}alkyl, aryl, $CONR^{88}R^{89}$, $NR^{90}R^{91}$, hydroxy, $OCOR^{92}$, $NHCOC_{0-6}$alkyl where alkyl is optionally substituted by OH, $NHCOCF_3$, $NHSO_2R^{93}$, and $NHCO_2R^{94}$;

R^{87} is hydrogen or C_{1-6}alkyl, C_{1-6}alkoxy, or halogen, or R^{87} together with $R^{5'}$ forms a group -AA- where AA is $(CR^{95}R^{96})_{ad}$ or AA is $(CR^{95}=CR^{96})_{ae}$-AB and AB is oxygen, sulfur, $CR^{95}=CR^{96}$, $CR^{95}=N$, $CR^{95}NR^{96}$ or N=N;

Z is an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulfur;

R^{88}, R^{89}, R^{90}, R^{91}, R^{92}, R^{95}, and R^{96} are independently hydrogen or C_{1-6}alkyl;

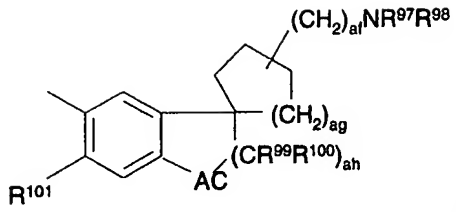
R^{93} and R^{94} are independently C_{1-6}alkyl;

ac is 0 to 4;

ad is 1, 2 or 3;

ae is 0, 1 or 2;

alternatively, E represents group (i):



(i);

R^{97} and R^{98} are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include C_{1-6}alkyl, aryl, $CONR^{102}R^{103}$, $NR^{104}R^{105}$, hydroxy, $OCOR^{106}$, $NHCOC_{0-6}$alkyl where alkyl is optionally substituted by OH, $NHCOCF_3$, $NHSO_2$ R^{107}, and $NHCO_2R^{108}$;

R^{99} and R^{100} are independently hydrogen or C1-6alkyl;

R^{101} is hydrogen or C_{1-6}alkyl or R^{101} and $R^{5'}$ together form a group -AD- where AD is $(CR^{109}R^{110})_{ai}$ or AD is $(CR^{109}R^{110})_{aj}$-AE and AE is oxygen, sulfur or $CR^{109}=CR^{110}$;

AC is oxygen, $CR^{111}R^{112}$ or NR^{113} or AC is a group $S(O)_{ak}$;

R^{102}, R^{103}, R^{104}, R^{105}, R^{106}, R^{109}, R^{110}, R^{111}, R^{112}, and R^{113} are independently hydrogen or C_{1-6}alkyl;

R^{107} and R^{108} are independently C1-6alkyl;

af is 0, 1, 2, 3, or 4;

ag is 1, 2, or 3;

ah is 1, 2, 3 or 4;

ai is 2, 3 or 4;

aj is 0, 1, 2, or 3; and

ak is 0, 1 or 2.

In another aspect, the present invention is to a method of treating CCR5 mediated disease states, including, but not limited to, COPD, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, atherosclerosis, sarcoidosis and other fibrotic disease, psoriasis, autoimmune diseases such as multiple sclerosis, and inflammatory bowel disease and HIV infection, all in mammals, preferably humans, comprising administering to such mammal in need thereof, an anilide of formula (I), or pharmaceutically active salts thereof.

In yet another aspect, the present invention is to pharmaceutical compositions comprising a compound of formula (I) and a pharmaceutically acceptable carrier therefor. In particular, the pharmaceutical compositions of the present invention are

used for treating CCR5-mediated disease states, including, but not limited to, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, atherosclerosis, sarcoidosis and other fibrotic disease, psoriasis, autoimmune diseases such as multiple sclerosis, inflammatory bowel disease, COPD and HIV all in mammals, preferably humans.

DETAILED DESCRIPTION OF THE INVENTION

It has now been discovered that substituted anilides of formula (I) are CCR5 receptor modulators. It has also now been discovered that selective inhibition of CCR5 receptor mechanisms by treatment with the receptor modulators of formula (I), or a pharmaceutically acceptable salt thereof, represents a novel therapeutic and preventative approach to the treatment of a variety of disease states, including, but not limited to, COPD, asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, atherosclerosis, sarcoidosis and other fibrotic disease, psoriasis, autoimmune diseases such as multiple sclerosis, and inflammatory bowel disease, all in mammals, preferably humans ("CCR5-mediated diseases"). Also, since CCR5 is a co-receptor for the entry of HIV into cells, selective receptor modulators may be useful in the treatment of HIV infection.

The term "alkyl" is used herein at all occurrences to mean a straight or branched chain radical of 1 to 6 carbon atoms, unless the chain length is limited thereto, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, and the like.

The terms "cycloalkyl" and "cyclic alkyl" are used herein at all occurrences to mean cyclic radicals, preferably comprising 3 to 7 carbon atoms which may be mono- or bicyclo-fused ring systems which may additionally include unsaturation, including, but not limited to, cyclopropyl, cyclopentyl, cyclohexyl, and the like.

The terms "halo" or "halogen" are used interchangeably herein at all occurrences to mean radicals derived from the elements chlorine, fluorine, iodine and bromine.

The term "heterocyclic ring" is used herein at all occurrences to mean a saturated or partially saturated 5-, 6-, or 7-membered ring system (unless the cyclic ring system is otherwise limited) in which the ring system contains one to 3 heteroatoms selected from oxygen, sulfur, or nitrogen, which ring system may be optionally substituted with C_{1-6}alkyl or C_{3-7}cycloalkyl. Examples of such rings include, but are not limited to, piperidine, tetrahydropyridine, and piperazine. When the heterocyclic ring is fused to a phenyl group, the term "heterocyclic ring", together with the phenyl ring to which it is fused, forms a ring which includes, but is not

limited to, 1,2,3,4-tetrahydroquinoline, 2-oxo-benzoxazole, 3,4-dihydro-3-oxo-1,4-benzoxazine, 3,4-dihydro-1,4-benzoxazine, and 2,3-dihydro-indole, which may be optionally substituted by C_{1-6}alkyl or oxo.

The term "6,6 or 6,5 bicyclic ring" means a 6,6 or 6,5-bicyclic ring system containing a nitrogen atom and optionally a further heteroatom selected from nitrogen, oxygen, or sulfur, which ring system may be optionally substituted with C_{1-6}alkyl. Examples of such ring systems include, but are not limited to, tropane, isoquinuclidine and granatane rings.

The term "CCR5 mediated disease state" is used herein at all occurrences to mean any disease state which is mediated (or modulated) by CCR5.

The term "monocyclic heterocyclic ring" is used herein at all occurrences to mean a single aromatic ring of 5 to 7 members containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulfur represented by P^1 and/or P^2 including thienyl, furyl, pyrrolyl, and pyridyl.

The term "fused bicyclic heterocyclic ring" is used herein at all occurrences to mean a fused bicyclic aromatic ring system of 8 to 11-members containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulfur including indole, benzofuran, benzothiophene, quinoline, and isoquinoline rings.

Suitably, pharmaceutically acceptable salts of formula (I) include, but are not limited to, salts with inorganic acids such as hydrochloride, sulfate, phosphate, diphosphate, hydrobromide, and nitrate, or salts with an organic acid such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate, palmitate, salicylate, and stearate.

The compounds of the invention can exist in unsolvated as well as solvated forms, including hydrated forms. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol, and the like, are equivalent to the unsolvated forms for purposes of this invention.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. The stereocenters may be of any combination of R and S configuration, for example, (R,R), (R,S), (S,S) or (S,R). All of these compounds are within the scope of the present invention.

It will be understood by one skilled in the art that for 3-aryl or 3-heteroaryl-2-propenanilides of this invention, the geometry around the propenoyl double bond is trans or (E) unless the geometry is specified to be cis or (Z).

For compounds of formula (I) various embodiments are as follows. It will be understood that the basic nitrogen in moiety E may be optionally quaternized with C_{1-6}alkyl or is optionally present as the N-oxide.

P^1 is suitably phenyl, fused bicyclic aryl, a 5- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulfur, or a fused bicyclic heterocyclic ring of 8 to 11 members containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulfur. Preferably, P^1 is phenyl, naphthyl, furyl, thienyl, pyridyl, indolyl, benzofuranyl, and benzothienyl. More preferably, P^1 is phenyl and naphthalenyl. .

When $R^{1'}$ is a 5- to 7-membered heterocyclic ring containing 1 to 4 heteroatoms selected from oxygen, nitrogen, or sulfur, suitable heterocyclic rings include aromatic groups such as thienyl, furyl, pyrrolyl, triazolyl, diazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyridyl, pyrimidyl, pyrazinyl, and dioxanyl. Saturated and partially saturated rings are also within the scope of the invention, in particular rings including an oxo or thioxo moiety such as lactams and thiolactams. Suitably, the heterocyclic ring can be linked to the remainder of the molecule via a carbon atom, or, when present, a nitrogen atom. Suitable substituents for these rings include one to two of $R^{32'}$.

L is suitably $CONR^{5'}$.

$R^{1'}$ and $R^{2'}$ are suitably independently hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{3-6}cycloalkenyl, $(CH_2)_b NR^{6'}R^{7'}$, $(CH_2)_a NR^{6'}COR^{8'}$, $(CH_2)b'_a NR^{6'}CO_2R^{9'}$, $(CH_2)_b NR^{6'}SO_2R^{10'}$, $(CH_2)_b CONR^{11'}R^{12'}$, hydroxy$C_{1-6}$alkyl, C_{1-4}alkoxyalkyl (optionally substituted by a C_{1-4}alkoxy or hydroxy group), $(CH_2)_b CO_2C_{1-6}$alkyl, $(CH_2)_c OC(O)R^{13'}$, $CR^{14'}{=}NOR^{15'}$, $CNR^{16'}{=}NOR^{15'}$, $COR^{17'}$, $CONR^{11'}R^{12'}$, $CONR^{11'}(CH_2)_d OC_{1-4}$alkyl, $CONR^{11'}(CH_2)_b CO_2R^{18'}$, $CONHNR^{19'}R^{20'}$, $CONR^{11'}SO_2R^{21'}$, $CO_2R^{22'}$, cyano, trifluoromethyl, $NR^{6'}R^{7'}$, $NR^{6'}COR^{8'}$, $NR^{23'}CO(CH_2)_b NR^{23'}R^{24'}$, $NR^{23'}CONR^{23'}R^{24'}$, $NR^{6'}CO_2R^{9'}$, $NR^{6'}SO_2R^{10'}$, $N{=}CNR^{23'}NR^{23'}R^{24'}$, nitro, hydroxy, C_{1-6}alkoxy, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, $OC(O)NR^{25'}R^{26'}$, $SR^{27'}$, $SOR^{28'}$, $SO_2R^{28'}$, $SO_2NR^{29'}R^{30'}$, halogen, C_{1-6}alkanoyl, $CO_2(CH_2)_b OR^{31'}$, or $R^{1'}$ is phenyl or $R^{1'}$ is a 5 to 7-membered heterocyclic ring containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulfur, which are optionally substituted by one or two of $R^{32'}$.

$R^{1'}$ may also suitably be an optionally substituted, fused carbocyclic ring of 5 to 7-members, which may be partly or wholly unsaturated, or $R^{1'}$ is an optionally substituted, fused heterocyclic ring of 5 to 7-members containing 1 to 4 heteroatoms selected from nitrogen, oxygen, or sulfur, which may be partly or wholly unsaturated. $R^{1'}$ is preferably hydrogen, C_{1-6}alkyl, a fused 3,4-(tetramethylene) moiety, or halogen; $R^{2'}$ is preferably hydrogen or halogen. $R^{1'}$ is more preferably halogen, $R^{2'}$ is more preferably halogen. Most preferably, $R^{1'}$ and $R^{2'}$ taken together are 3,4-dichloro or 3,5-dichloro.

$R^{3'}$ is suitably hydrogen or C_{1-6}alkyl. Preferably, $R^{3'}$ is hydrogen.

$R^{4'}$ is suitably hydrogen, C_{1-6}alkyl, C_{1-6}alkylCONH, or halogen. Preferably, $R^{4'}$ is hydrogen;.

$R^{5'}$ is suitably hydrogen or C_{1-6}alkyl. Preferably $R^{5'}$ is hydrogen.

$R^{14'}$, $R^{15'}$, $R^{16'}$ $R^{17'}$, $R^{18'}$, $R^{19'}$ $R^{20'}$, $R^{23'}$, $R^{24'}$, $R^{27'}$, and $R^{31'}$ are suitably independently hydrogen or C_{1-6}alkyl.

$R^{6'}$ and $R^{7'}$ are suitably independently hydrogen or C_{1-6}alkyl, or $R^{6'}$ and $R^{7'}$ together with the nitrogen to which they are attached, forms a 5- to 6-membered heterocyclic ring, which may optionally be substituted by an oxo group, and, when there are six members, may optionally contain in the ring one oxygen or one sulfur atom.

$R^{8'}$ is suitably hydrogen, C_{1-6}alkyl or C_{1-4}alkoxyalkyl.

$R^{9'}$, $R^{21'}$, and $R^{28'}$ are suitably independently C_{1-6}alkyl.

$R^{10'}$ is suitably C_{1-6}alkyl or phenyl.

$R^{11'}$ and $R^{12'}$ are suitably independently hydrogen or C_{1-6}alkyl, or $R^{11'}$ and $R^{12'}$ together with the nitrogen to which they are attached form a 5- to 6-membered saturated heterocyclic ring which, when there are 6 ring members, may optionally contain in the ring one oxygen or one sulfur atom.

$R^{13'}$ is suitably C_{1-4}alkyl, optionally substituted by a C_{1-6}alkoxy.

$R^{22'}$ is suitably hydrogen or C_{1-6}alkyl optionally substituted with one or two substituents selected from C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, or $NR^{6'}R^{7'}$.

$R^{25'}$ and $R^{26'}$ are suitably independently hydrogen or C_{1-6}alkyl, or $R^{25'}$ and $R^{26'}$ together with the nitrogen to which they are attached form a 5- to 6-membered heterocyclic ring which, when there are six ring members, may optionally contain in the ring one oxygen or sulfur atom.

$R^{29'}$ and $R^{30'}$ are suitably independently hydrogen or C_{1-6}alkyl, or $R^{29'}$ and $R^{30'}$ together with the nitrogen to which they are attached form 5- to

6-membered heterocyclic ring which, when there are six ring members, may optionally contain in the ring one oxygen or sulfur atom.

$R^{32'}$ is suitably hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylOC_{1-6}alkyl, $CONR^{33'}R^{34'}$, $CO_2R^{35'}$, cyano, aryl, trifluoromethyl, $NR^{36'}R^{37'}$, nitro, hydroxy, C_{1-6}alkoxy, C_{1-6}alkanoyl, acyloxy, or halogen.

$R^{33'}$, $R^{34'}$, $R^{35'}$, $R^{36'}$, and $R^{37'}$ are suitably independently hydrogen or C_{1-6}alkyl.

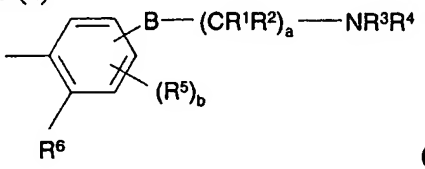
a' is suitably 1, 2, or 3.

b' is suitably 1, 2, 3 or 4.

c' is suitably 0, 1, 2 or 3.

d' is suitably 1, 2 or 3.

E suitably represents (a):



(a);

wherein:

B is suitably oxygen, $S(O)_c$, $CR^7{=}CR^8$, or CR^7R^8, or B is NR^9. B is preferably CR^7R^8, or oxygen. More preferably, B is CH_2 or oxygen.

R^1 and R^2 are suitably independently hydrogen or C_{1-6}alkyl. Preferably, R^1 and R^2 are hydrogen. Alternatively, $B(CR^1R^2)_a$ is $OCR^1R^2CR^1(OH)CR^1R^2$ or $OCR^1R^2CR^1(OCOCH_3)CR^1R^2$. Preferably, when $B(CR^1R^2)_a$ is $OCR^1R^2CR^1(OCOCH_3)CR^1R^2$, R^1 and R^2 are hydrogen.

R^3 and R^4 are suitably independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include C_{1-6}alkyl, aryl, $CONR^{10}R^{11}$, $NR^{10}R^{11}$, hydroxy, $OCOR^{12}$, $NHCOC_{0-6}$alkyl where alkyl is optionally substituted by OH, $NHCOCF_3$, $NHSO_2R^{13}$, and $NHCO_2R^{14}$. Preferably R^3 and R^4 are both C_{1-6}alkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur. More preferably, R^3 and R^4 are C_{3-6}alkyl, or together with the

nitrogen to which they are attached form a 6-membered ring, optionally substituted with one or more of C_{1-6}alkyl, N-acetamido, or hydroxy. Most preferably, R^3 and R^4 are both isopropyl or R^3 is isopropyl and R^4 is tert-butyl, or together with the nitrogen to which they are attached are 1-(2,2,6,6-tetramethylpiperidinyl), 1-(4-acetamido-2,2,6,6-tetramethylpiperidinyl), 1-(4-hydroxy-2,2,6,6-tetramethylpiperidinyl), or 1-(4-hydroxy-2,2,4,6,6-pentamethylpiperidinyl).

Preferably, B-$(CR^1R^2)_a$-NR^3R^4 is ortho to R^5, meta to L and para to R^6, and R^5 is para to L.

R^5 is suitably hydrogen, C_{1-6}alkyl, aryl, CN, $CONR^{15}R^{16}$, CO_2R^{17}, trifluoromethyl, $NHCO_2R^{18}$, hydroxy, C_{1-6}alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, OCF_3, $S(O)_dR^{19}$, $SO_2NR^{20}R^{21}$, or halogen. R^5 is preferably C_{1-6}alkoxy, SC_{1-6}alkyl or halogen; more preferably methoxy, methylthio or iodo, most preferably methoxy. When R^5 is methoxy, it is preferably para to L.

R^6 is suitably hydrogen, C_{1-6}alkyl, aryl, trifluoromethyl, hydroxy, C_{1-6}alkoxy, or halogen, or R^6 taken together with $R^{5'}$ forms a group D where D is $(CR^{22}R^{23})_e$ or D is $(CR^{22}R^{23})_f$-G where G is oxygen, sulfur, or $CR^{22}=CR^{23}$, $CR^{22}=N$, $=CR^{22}O$, $=CR^{22}S$, or $=CR^{22}$-NR^{23}. Preferably, R^6 is hydrogen.

R^7, R^8, R^{10}, R^{11}, R^{12}, R^{15}, R^{16}, R^{17}, R^{20}, R^{21}, R^{22}, and R^{23} are suitably independently hydrogen or C_{1-6}alkyl.

R^9 is suitably hydrogen, C_{1-6}alkyl, or phenylC_{1-6}alkyl.

R^{13}, R^{14}, R^{18}, and R^{19} are suitably independently C_{1-6}alkyl.

a is suitably 1, 2, 3, or 4. Preferably, a is 2 or 3, more preferably, a is 2 or 3 when B is oxygen and a is 2 when B is CH_2, most preferably, a is 2 when B is oxygen.

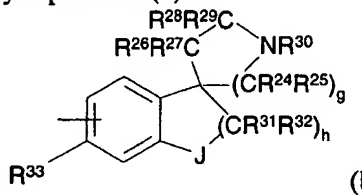
b is suitably 1 or 2. Preferably, b is 1.

c and d are suitably independently 0, 1, or 2.

e is suitably 2, 3, or 4.

f is suitably 0, 1, 2, or 3.

alternatively, E suitably represents (b):



(b);

R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{31}, and R^{32} are suitably independently hydrogen or C_{1-6}alkyl. R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{31}, and R^{32} are preferably hydrogen.

R^{30} is suitably hydrogen, C_{1-6}alkyl, or C_{3-7}cycloalkyl. Preferably, R^{30} is C_{1-6}alkyl, more preferably, R^{30} is C_{3-6}alkyl, most preferably, R^{30} is isopropyl.

R^{33} is suitably hydrogen, C_{1-6}alkyl, trifluoromethyl, hydroxy or halogen, or R^{33} and $R^{5'}$ together form a group -K- where K is $(CR^{34}R^{35})_i$ or K is $(CR^{34}R^{35})_j$ -M and M is oxygen, sulfur, $CR^{34}=CR^{35}$, $CR^{34}=N$, or N=N. Preferably, R^{33} is hydrogen.

J is suitably oxygen, $CR^{36}R^{37}$, or NR^{38}, or J is a group $S(O)_k$. Preferably, J is oxygen. Preferably, J is para to L.

R^{34}, R^{35}, R^{36}, R^{37}, R^{38} are suitably independently hydrogen or C_{1-6}alkyl.

g is suitably 1, 2, or 3. Preferably, g is 2 or 3, more preferably 2.

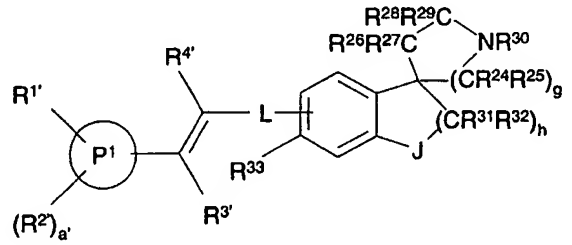
h is suitably 1, 2, or 3. Preferably, h is 1.

i is suitably 2, 3, or 4.

j is suitably 0, 1, 2, or 3.

k is suitably 0, 1 or 2.

A preferred subgenus of the compounds of formula (I) are compounds of formula (Ia) in which $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, P^1, a', L, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, J, g, and h are defined as above:



Formula (Ia)

Among the preferred compounds of this invention are the following compounds:

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-phenyl-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3,4-dichlorophenyl)-2-propenamide;

N-[4-Methoxy-3-[(2S)-(1-methyl-2-pyrrolidinyl)methoxy]phenyl]-3-(4-methylphenyl)-2-propenamide;

N-[4-Methoxy-3-[(2S)-(1-methyl-2-pyrrolidinyl)methoxy]phenyl]-3-(3,4-dichlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(4-chlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3,4-difluorophenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2-naphthalenyl)-2-propenamide hydrochloride;

N-[3-[2-(2,2,6,6-Tetramethylpiperidin-1-yl)ethoxy]-4-methoxyphenyl]-3-(3,4-dichlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3,4-dichlorophenyl)-2-propenamide;

N-[1-[2-[Bis(1-methylethyl)amino]ethyl]-1,2,3,4-tetrahydroquinol-7-yl]-3-(3,4-dichlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3-chlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3-chlorophenyl)-2-propenamide;

N-[3-[2-(cis-2,6-Dimethylpiperidin-1-yl)ethoxy]-4-methoxyphenyl]-3-(3-chlorophenyl)-2-propenamide;

N-[3-[2-(N-Cyclohexyl-N-isopropylamino)ethoxy]-4-methoxyphenyl]-3-(3-chlorophenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(4-chlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(4-chlorophenyl)-2-propenamide;

N-[3-[2-(cis-2,6-Dimethylpiperidin-1-yl)ethoxy]-4-methoxyphenyl]-3-(4-chlorophenyl)-2-propenamide;

N-[3-[2-(N-Cyclohexyl-N-isopropylamino)ethoxy]-4-methoxyphenyl]-3-(4-chlorophenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methylphenyl]-3-[(3,4-methylenedioxy)phenyl]-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-[(3,4-methylenedioxy)phenyl]-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-[(3,4-methylenedioxy)phenyl]-2-propenamide;

N-[3-[2-(N-Cyclohexyl-N-isopropylamino)ethoxy]-4-methoxyphenyl]-3-[(3,4-methylenedioxy)phenyl]-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3,4-difluorophenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methylphenyl]-3-(3,4-difluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3,4-difluorophenyl)-2-propenamide;

N-[3-[2-(cis-2,6-Dimethylpiperidin-1-yl)ethoxy]-4-methoxyphenyl]-3-(3,4-difluorophenyl)-2-propenamide;

N-[3-[2-(N-Cyclohexyl-N-isopropylamino)ethoxy]-4-methoxyphenyl]-3-(3,4-difluorophenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methylphenyl]-3-(2-naphthalenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(2-naphthalenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2-naphthalenyl)-2-propenamide;

N-[3-[2-(N-Cyclohexyl-N-isopropylamino)ethoxy]-4-methoxyphenyl]-3-(2-naphthalenyl)-2-propenamide;

(E)-N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3-chlorophenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethyl]-2-oxo-(3H)-benzoxazol-5-yl]-3-(3,4-dichlorophenyl)-2-propenamide;

N-[4-[2-[Bis(1-methylethyl)amino]ethyl]-3,4-dihydro-3-oxo-2H-1,4-benzoxazin-6-yl]-3-(3,4-dichlorophenyl)-2-propenamide;

N-[4-[2-[Bis(1-methylethyl)amino]ethyl]-3,4-dihydro-2H-1,4-benzoxazin-6-yl]-3-(3,4-dichlorophenyhl-2-propenamide;

N-[2,3-Dihydro-1-[2-[bis(1-methylethyl)amino]ethyl]-1H-indol-6-yl]-3-(3,4-dichlorophenyl)-2-propenamide;

(E)-N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(5-indolyl)-2-propenamide;

(E)-N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl)-3-(6-indolyl)-2-propenamide;

(E)-•••-Dimethyl-N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-phenyl-2-propenamide;

(Z)-N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl)-•-(acetylamino)-3-(3,4-dichlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3,4-dichlorophenyl)]-2-propenamide;

(E)-N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(5,6,7,8-tetrahydronaphth-2-yl)-2-propenamide trifluoroacetate salt;

N-(Spiro[benzofuran-3(2H),4'-piperidin]-5-yl)-3-(3,4-dichlorophenyl)-2-propenamide;

N-[1'-(Isopropyl)spiro[benzofuran-3(2H)4'-piperidin]-5-yl]-3-(3,4-dichlorophenyl)-2-propenamide;

(E)-N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(4-chloro-3-methylphenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxypheny]-3-(4-fluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-[4-(trifluoromethyl)phenyl]-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-[3-(trifluoromethyl)phenyl]-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-[3-(trifluoromethyl)phenyl]-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-[3-(trifluoromethyl)phenyl]-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2-chlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(2-chlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2-chlorophenyl)]-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2,4-dichlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(2,4-dichlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2,4-dichlorophenyl)]-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2,6-dichlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(2,6-dichlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2,6-dichlorophenyl)]-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3,5-difluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3,5-difluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3,5-difluorophenyl)]-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2,5-difluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(2,5-difluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2,5-difluorophenyl)]-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2,4-difluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(2,4-difluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2,4-difluorophenyl)]-2-propenamide(SB-383258);

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3-fluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3-fluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3-fluorophenyl)]-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2-chloro-6-fluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(2-chloro-6-fluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2-chloro-6-fluorophenyl)]-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(4-bromo-2-fluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(4-bromo-2-fluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(4-bromo-2-fluorophenyl)]-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(4-chloro-2-fluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(4-chloro-2-fluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(4-chloro-2-fluorophenyl)]-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2-chloro-4-fluorophenyl)-2-propenamide

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(2-chloro-4-fluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2-chloro-4-fluorophenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2,6-difluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(2,6-difluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2,6-difluorophenyl)]-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(4-bromophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(4-bromophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(4-bromophenyl)]-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(4-chloro-3-nitrophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(4-chloro-3-nitrophenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-[4-(1-methylethyl)phenyl]-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-[4-(1-methylethyl)phenyl]-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-[4-(1-methylethyl)phenyl]-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(5-bromo-2-methoxyphenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(5-bromo-2-methoxyphenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-([1,1'-biphenyl]-4-yl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-([1,1'-biphenyl]-4-yl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2,3-dihydro-1H-inden-5-yl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3-bromo-4-fluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3-bromo-4-fluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3-bromo-4-fluorophenyl)]-2-propenamide;

(E)-N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3,5-dichlorophenyl)-2-propenamide trifluoroacetate;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3,5-dichlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3,5-dichlorophenyl)]-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3,4-dimethylphenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3,4-dimethylphenyl)-2-propenamide

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3,4-dimethylphenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(4-cyanophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(4-cyanophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(4-cyanophenyl)]-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2-fluoro-3-phenyl-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-2-fluoro-3-phenyl-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-2-fluoro-3-phenyl-2-propenamide;

(E)-N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-[4-chloro-3-(trifluoromethyl)phenyl]-2-propenamide;

(E)-N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3,4-dichlorophenyl)-•-methyl-2-propenamide;

(E)-N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-[4-(trifluoromethyl)phenyl]-2-propenamide;

N-[3-[2-Acetoxy-3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3,4-dichlorophenyl)-2-propenamide;

N-[3-[2-(4-Hydroxy-2,2,6,6-tetramethylpiperidin-1-yl)ethoxy]-4-methoxyphenyl]-3-(3,4-dichlorophenyl)-2-propenamide;

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H)4'-piperidin]-5-yl]-3-(3,5-dichlorophenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3-thienyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3-thienyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3-thienyl)-2-propenamide;

N-[3-[2-(cis-2,6-Dimethylpiperidin-1-yl)ethoxy]-4-methoxyphenyl]-3-(3-thienyl)-2-propenamide;

N-[3-[2-(N-Cyclohexyl-N-isopropylamino)ethoxy]-4-methoxyphenyl]-3-(3-thienyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methylphenyl]-3-(4-pyridinyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(4-pyridinyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3-furanyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methylphenyl]-3-(3-furanyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3-furanyl)-2-propenamide;

N-[3-[2-(cis-2,6-Dimethylpiperidin-1-yl)ethoxy]-4-methoxyphenyl]-3-(3-furanyl)-2-propenamide;

N-[3-[2-(N-Cyclohexyl-N-isopropylamino)ethoxy]-4-methoxyphenyl]-3-(3-furanyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(2-thienyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2-thienyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2-furanyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(1H-indol-3-yl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(1H-indol-2-yl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(1-methyl-1H-indol-2-yl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(benzo[b]thien-3-yl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2-benzofuranyl)-2-propenamide; and

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(benzo[b]thien-2-yl)-2-propenamide.

Among the more preferred compounds of this invention are the following compounds:

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-phenyl-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3,4-dichlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3,4-difluorophenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2-naphthalenyl)-2-propenamide hydrochloride;

N-[3-[2-(2,2,6,6-Tetramethylpiperidin-1-yl)ethoxy]-4-methoxyphenyl]-3-(3,4-dichlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3,4-dichlorophenyl)-2-propenamide;

N-[1-[2-[Bis(1-methylethyl)amino]ethyl]-1,2,3,4-tetrahydroquinol-7-yl]-3-(3,4-dichlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3-chlorophenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(4-chlorophenyl)-2-propenamide;

N-[3-[2-(N-Cyclohexyl-N-isopropylamino)ethoxy]-4-methoxyphenyl]-3-(4-chlorophenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3,4-difluorophenyl)-2-propenamide;

N-[3-[2-(cis-2,6-Dimethylpiperidin-1-yl)ethoxy]-4-methoxyphenyl]-3-(3,4-difluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(2-naphthalenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2-naphthalenyl)-2-propenamide;

N-[3-[2-(N-Cyclohexyl-N-isopropylamino)ethoxy]-4-methoxyphenyl]-3-(2-naphthalenyl)-2-propenamide;

(E)-N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3-chlorophenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethyl]-2-oxo-(3H)-benzoxazol-5-yl]-3-(3,4-dichlorophenyl)-2-propenamide;

N-[4-[2-[Bis(1-methylethyl)amino]ethyl]-3,4-dihydro-3-oxo-2H-1,4-benzoxazin-6-yl]-3-(3,4-dichlorophenyl)-2-propenamide;

N-[2,3-Dihydro-1-[2-[bis(1-methylethyl)amino]ethyl]-1H-indol-6-yl]-3-(3,4-dichlorophenyl)-2-propenamide;

(E)-N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(5,6,7,8-tetrahydronaphth-2-yl)-2-propenamide trifluoroacetate salt;

N-[1'-(Isopropyl)spiro[benzofuran-3(2H)4'-piperidin]-5-yl]-3-(3,4-dichlorophenyl)-2-propenamide;

(E)-N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(4-chloro-3-methylphenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3,5-difluorophenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(4-bromophenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3-bromo-4-fluorophenyl)-2-propenamide;

(E)-N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3,5-dichlorophenyl)-2-propenamide trifluoroacetate;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3,5-dichlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3,5-dichlorophenyl)]-2-propenamide;

N-[3-[2-Acetoxy-3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3,4-dichlorophenyl)-2-propenamide;

N-[3-[2-(4-Hydroxy-2,2,6,6-tetramethylpiperidin-1-yl)ethoxy]-4-methoxyphenyl]-3-(3,4-dichlorophenyl)-2-propenamide; and

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H)4'-piperidin]-5-yl]-3-(3,5-dichlorophenyl)-2-propenamideAmong the most preferred compounds of this invention are the following compounds:

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3,4-dichlorophenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2-naphthalenyl)-2-propenamide hydrochloride;

N-[3-[2-(2,2,6,6-Tetramethylpiperidin-1-yl)ethoxy]-4-methoxy-phenyl]-3-(3,4-dichlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3,4-dichlorophenyl)-2-propenamide;

N-[3-[2-(4-Hydroxy-2,2,6,6-tetramethylpiperidin-1-yl)ethoxy]-4-methoxyphenyl]-3-(3,4-dichlorophenyl)-2-propenamide; and

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H)4'-piperidin]-5-yl]-3-(3,5-dichlorophenyl)-2-propenamide.

Among compounds excluded from this invention are the following compounds:

N-[4-Methoxy-3-[(2S)-(1-phenylmethyl-2-pyrrolidinyl)methoxy]phenyl]-3-(3,4-dichlorophenyl)-2-propenamide-;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3,4-methylenedioxyphenyl)-2-propenamide;

N-[3-[2-(cis-2,6-Dimethylpiperidin-1-yl)ethoxy]-4-methoxyphenyl]-3-(3,4-methylenedioxyphenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methylphenyl]-3-(4-chlorophenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3-pyridinyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3-pyridinyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3-pyridinyl)-2-propenamide;

N-[3-[2-(cis-2,6-Dimethylpiperidin-1-yl)ethoxy]-4-methoxyphenyl]-3-(3-pyridinyl)-2-propenamide;

N-[3-[2-(N-Cyclohexyl-N-isopropylamino)ethoxy]-4-methoxyphenyl]-3-(3-pyridinyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(4-pyridinyl)-2-propenamide;

N-[3-[2-(cis-2,6-Dimethylpiperidin-1-yl)ethoxy]-4-methoxyphenyl]-3-(1H-imidazol-4-yl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methylphenyl]-3-(3-pyridinyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(4-pyridinyl)-2-propenamide;

N-[3-[2-(cis-2,6-Dimethylpiperidin-1-yl)ethoxy]-4-methoxyphenyl]-3-(4-pyridinyl)-2-propenamide;

N-[3-[2-(N-Cyclohexyl-N-isopropylamino)ethoxy]-4-methoxyphenyl]-3-(4-pyridinyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3-furanyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2-thienyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methylphenyl]-3-(2-thienyl)-2-propenamide;

N-[3-[2-(cis-2,6-Dimethylpiperidin-1-yl)ethoxy]-4-methoxyphenyl]-3-(2-thienyl)-2-propenamide;

N-[3-[2-(N-Cyclohexyl-N-isopropylamino)ethoxy]-4-methoxyphenyl]-3-(2-thienyl)-2-propenamide; and

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(1H-imidazol-4-yl)-2-propenamide.

Known compounds overlapping with the scope of the instant invention are as follows.

A subgenus of formula (I) wherein: E is (a); B is meta to L; B-$CR^1R^2)_a$-NR^3R^4 is O-$(CH_2)_3$-N$(CH_3)_2$; L is CONH; R^5, R^6, $R^{1'}$, $R^{2'}$, $R^{3'}$, and $R^{4'}$ are hydrogen; and P^1 is phenyl.

A further known subgenus of formula (I) is wherein:E is (a); B is para to L; B-$(CR^1R^2)_a$-NR^3R^4 is S-$(CH_2)_3$-N$(CH_3)_2$; L is CONH; R5, R^6, $R^{1'}$, $R^{2'}$, $R^{3'}$, and $R^{4'}$ are hydrogen; and P^1 is phenyl.

Still a further known subgenus of formula (I) is wherein:E is (a); B-$(CR^1R^2)_a$-NR^3R^4 is ortho to L; B is CH_2, NCH_3, oxygen, S, or SO_2; R^1 and R^2 are hydrogen or methyl; a is 0-4; R^3 and R^4 are independently hydrogen, C_{1-3}alkyl, benzyl, or R^3 and R^4 taken together with the nitrogen to which they are attached form a pyrrolidinyl, piperidinyl, morpholino, and (4-methyl-1-piperazinyl), (4-phenyl-1-piperazinyl), [4-(2-methoxyphenyl)-1-piperazinyl], [4-(4-methoxyphenyl)-1-piperazinyl], or [(4-fluorophenyl)-1-piperazine] ring; NR^3R^4 is also present as a methochloride quaternary salt; R^5 is hydrogen, methyl, acetyl, trifluoromethyl, nitro, methoxy, or chloro; L is $CONR^{5'}$; $R^{3'}$ is hydrogen; $R^{4'}$ is hydrogen or C_{1-4}alkyl; $R^{5'}$ is hydrogen or C_{1-2}alkyl; P^1 is phenyl or 2-thienyl; and $R^{1'}$ and $R^{2'}$ are independently hydrogen, methyl, trifluoromethyl, methoxy, fluoro, or chloro, all of which have been described in United States Patent 3,167,556, published January 26, 1965, United States Patent 3,201,401, published August 17, 1965, GB 1099829, published 17 January 1968, and Krapcho, et al., *J. Med. Chem.*, 1969, 12, 164-6 as 5-HT inhibitors, and reported to have 5-HT inhibitory activity, and have been described in JP 05255291, published 5 October 1993, and reported to have calcium antagonist activity.

A compound of formula (I) wherein: E is (a); B is para to L; B-$(CR^1R^2)_a$ NR^3R^4 is O-$(CH_2)_2$-N$(Et)_2$; L is CONH; $R^{1'}$ is 5-nitro; R^5, R^6, $R^{2'}$, $R^{3'}$, and $R^{4'}$ are hydrogen; and P^1 is 2-furyl, has been described in JP 45006533, published 5 March 1970, and reported to have anti-cancer activity.

A compound of formula (I) wherein: E is (a); B is para to L; B-$(CR^1R^2)_a$ NR^3R^4 is O-$CH_2CH(OH)CH_2$-NH-tert-butyl; L is CONH; R^6, $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, and $R^{5'}$ are hydrogen; R^5 is 3-ethyl; and P^1 is phenyl, has been described in ZA 6805360, published 19 February 1970, and reported to have •-adrenergic blocking activity.

A compound of formula (I) wherein: E is (a); B is para to L;

B-$(CR^1R^2)_a$ NR^3R^4 is O-$(CH_2)_2$-(1-pyrrolidine); L is CONH; $R^{2'}$, $R^{3'}$, $R^{4'}$, and R^6 are hydrogen; R^5 is 3,5-dimethyl; $R^{1'}$ is 2-methyl; and P^1 is phenyl, have been described in DE 4036782, published 21 May 1992, as an antiarrhythmic.

A subgenus of formula (I) wherein: E is (c); Q is ortho to L; Q-$(CR^{39}R^{40})_1$-R^{41} is –$(CH_2)_{2-3}$-(2-piperidinyl); R^{47} is methyl or ethyl; R^{42} is hydrogen or methoxy; R^{43}, $R^{1'}$, $R^{2'}$ and $R^{3'}$ are hydrogen; L is $CONR^{5'}$; $R^{4'}$ and $R^{5'}$ are independently hydrogen or methyl; P^1 is phenyl, have been described in United States Patent 3,931,195, published January 6, 1976, and United States Patent 4,000,143, published December 28, 1976, as antiserotonin agents

A subgenus of formula (I) wherein: E is (g); R^{71} is meta to L; R^{71} is (C_{0-1}alkyl-1-piperazine); R^{72} is 4-methoxy; $R^{1'}$ is bromo, phenyl, or 4-pyridinyl; R^{73}, $R^{2'}$, $R^{3'}$, and $R^{4'}$ are hydrogen; L is CONH; P^1 is phenyl or 3-thienyl,have been described in international patent application WO 95/06044, published 2 March 1995, as 5-HT1D receptor antagonists.

Formulation of Pharmaceutical Compositions

The pharmaceutically effective compounds of this invention (and the pharmaceutically acceptable salts thereof) are administered in conventional dosage forms prepared by combining a compound of formula (I) ("active ingredient") in an amount sufficient to treat asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, atherosclerosis, sarcoidosis and other fibrotic diseases, psoriasis, autoimmune diseases such as multiple sclerosis, inflammatory bowel disease, COPD, and HIV infection, with standard pharmaceutical carriers or diluents according to conventional procedures well known in the art. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax.

A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25 mg to about 1000 mg.

When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

The active ingredient may also be administered topically to a mammal in need of treatment or prophylaxis of CCR5 mediated disease states. The amount of active ingredient required for therapeutic effect on topical administration will, of course, vary with the compound chosen, the nature and severity of the disease state being treated and the mammal undergoing treatment, and is ultimately at the discretion of the physician. A suitable dose of an active ingredient is 1.5 mg to 500 mg for topical administration, the most preferred dosage being 1 mg to 100 mg, for example 5 to 25 mg administered two or three times daily.

By topical administration is meant non-systemic administration and includes the application of the active ingredient externally to the epidermis, to the buccal cavity and instillation of such a compound into the ear, eye and nose, and where the compound does not significantly enter the blood stream. By systemic administration is meant oral, intravenous, intraperitoneal and intramuscular administration.

While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, e.g. from 1% to 2% by weight of the formulation although it may comprise as much as 10% w/w but preferably not in excess of 5% w/w and more preferably from 0.1% to 1% w/w of the formulation.

The topical formulations of the present invention, both for veterinary and for human medical use, comprise an active ingredient together with one or more acceptable carrier(s) therefor and optionally any other therapeutic ingredient(s). The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams; ointments or pastes, and drops suitable for administration to the eye, ear or nose.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a suitable aqueous or alcoholic solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining

at 98-100°C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy basis. The basis may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of natural origin such as almond, corn, arachis; castor or olive oil; wool fat or its derivatives, or a fatty acid such as stearic or oleic acid together with an alcohol such as propylene glycol. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums, cellulose derivatives or inorganic materials such as silicaceous silicas, and other ingredients such as lanolin, may also be included.

The active ingredient may also be administered by inhalation. By "inhalation" is meant intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques. The daily dosage amount of the active ingredient administered by inhalation is from about 0.1 mg to about 100 mg per day, preferably about 1 mg to about 10 mg per day.

In one aspect, this invention relates to a method of treating asthma and atopic disorders (for example, atopic dermatitis and allergies), rheumatoid arthritis, atherosclerosis, sarcoidosis and other fibrotic diseases, psoriasis, autoimmune diseases such as multiple sclerosis, inflammatory bowel disease, COPD, and HIV infection, all in mammals, preferably humans, which comprises administering to

such mammal an effective amount of a CCR5 receptor modulator, in particular, a compound as depicted in formula (I).

By the term "treating" is meant either prophylactic or therapeutic therapy. Such formula (I) compound can be administered to such mammal in a conventional dosage form prepared by combining the formula (I) compound with a conventional pharmaceutically acceptable carrier or diluent according to known techniques. It will be recognized by one of skill in the art that the form and character of the pharmaceutically acceptable carrier or diluent is dictated by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The formula (I) compound is administered to a mammal in need of treatment for CCR5-mediated diseases in an amount sufficient to decrease symptoms associated with these diseases. The route of administration may be oral or parenteral.

The term parenteral as used herein includes intravenous, intramuscular, subcutaneous, intra-rectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. The daily parenteral dosage regimen will preferably be from about 30 mg to about 300 mg per day of active ingredient. The daily oral dosage regimen will preferably be from about 100 mg to about 2000 mg per day of active ingredient.

It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a formula (I) compound will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular mammal being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of the formula (I) compound given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

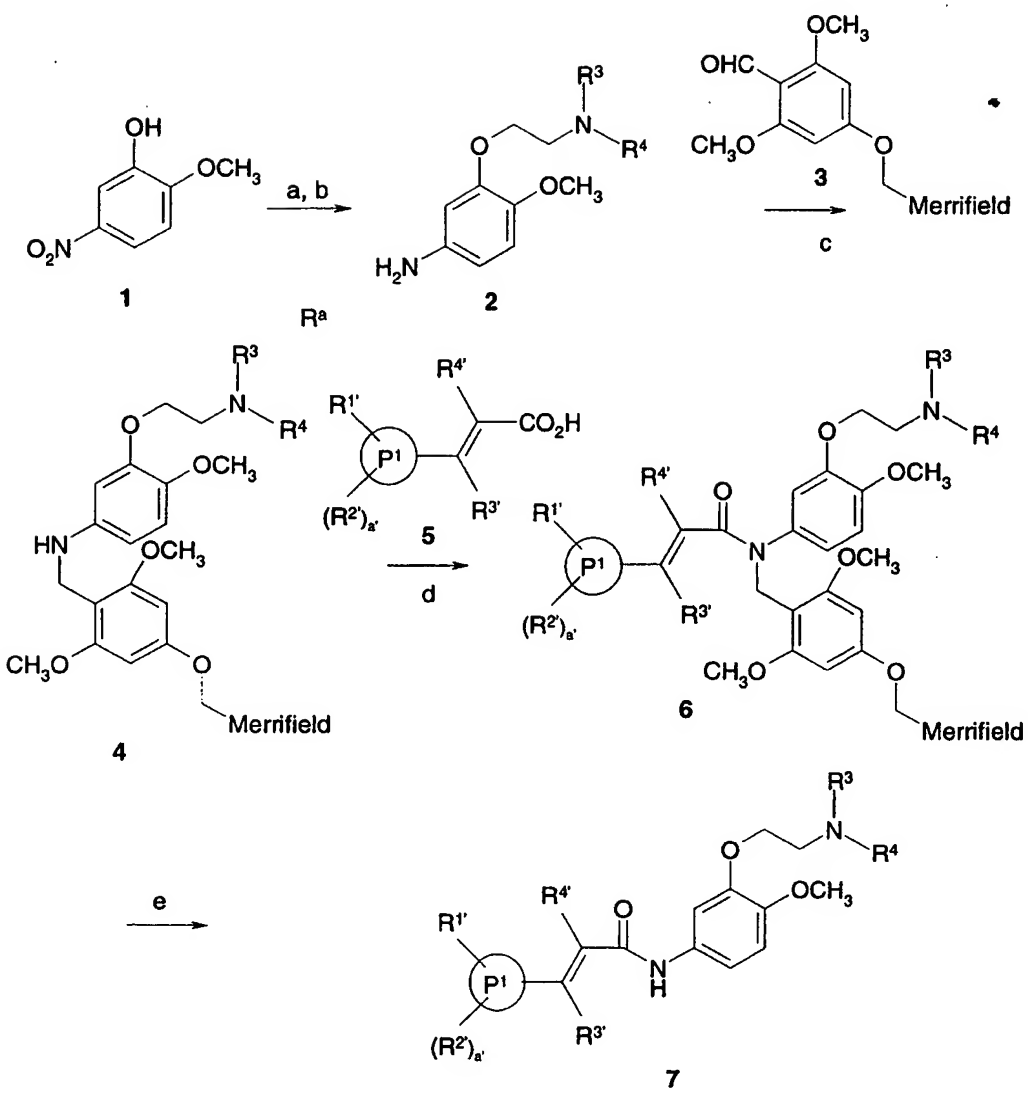
Methods of Preparation

Compounds of formula (I) are prepared by condensing suitably substituted 3-aryl or heteroaryl-2-propenoic acids and suitably substituted anilines, which are commercially available or synthesized by methods known to the art from commercially available starting materials, using methods known to the art. For example, suitably substituted 3-aryl or heteroaryl-2-propenoic acids are treated with a suitable reagent, such as thionyl chloride, at a suitable temperature, such as at reflux, to afford 3-aryl or heteroaryl-2-propenoyl chlorides, and the 3-aryl or heteroaryl-2-propenoyl chlorides are condensed with suitably substituted anilines in

the presence of a suitable base, such as diisopropylethylamine, in a suitable solvent, such as dichloromethane, to give compounds of formula (I). Many additional methods for converting a carboxylic acid to an amide are known, and can be found in standard reference books, such as "Compendium of Organic Synthetic Methods", Vol. I-VI (published by Wiley-Interscience).

Compounds of this invention were also prepared using solid-phase chemistry as described in Scheme 1 and using the general method described in international patent application WO 99/01127, published 14 January 1999. Appropriately substituted 3-[2-(alkylamino)ethoxy]anilines **1-2**, such as 3-[2-(diisopropylamino)ethoxy]-4-methoxyaniline, synthesized from commercially available 2-methoxy-5-nitrophenol, **I-1**, according to the procedures described in WO 99/01127, is attached to a polymer support such as Merrifield resin-bound aldehyde **I-3**, following the general protocol of Boojamra et al., (*J. Org. Chem.*, **1995**, 60, 5742-3) by reductive amination employing a suitable reducing agent, such as sodium triacetoxyborohydride, in a suitable solvent, such as dimethylformamide containing 1% acetic acid, to give **1-4**. The resin-bound aniline **1-4** is acylated with a commercially available or synthetically accessible 3-aryl- or heteroaryl-2-propenoic acid **I-5**, for example, 3-(3,4-dichlorophenyl)-2-propenoic acid, using, for example, N-bromosuccinimide and triphenylphosphine in dichloromethane, or in dichloromethane in combination with dimethylformamide, in the presence of an organic base such as pyridine to afford **I-6**. For example, **1-4** is treated with a ten-fold excess of an equimolar mixture of a 3-aryl- or heteroaryl-2-propenoic acid, triphenylphosphine and N-bromosuccinimide, in a suitable solvent, such as dichloromethane, after which a ten-fold excess of a suitable base, such as pyridine, is added, and the mixture is gently agitated for a suitable time, for example, forty-eight hours, to afford the resin-bound amide **1-6**. Optionally, dimethylformamide may be added to the resulting mixture to increase the solubility of the 3-aryl- or heteroaryl-2-propenoic acid. Alternatively, **I-5** is converted to the acid chloride, for example by heating with thionyl chloride, and the acid chloride is condensed with **I-4** to afford **I-6**. Treatment of **1-6** with a suitable acid in a suitable solvent, such as trifluoroacetic acid:dichloromethane:water (50:48:2) gives 3-aryl- or heteroaryl-2-propenamides **1-7** which are compounds of formula (I).

Scheme I:



(a) $Cl(CH_2)_2NR^3R^4$, K_2CO_3, CH_3COCH_3; (b) H_2, 5% Pd/C, MeOH; (c) Merrifield resin bound aldehyde (3), $NaBH(OAc)_3$, 1% HOAc/DMF; (d) 3-aryl- or heteroaryl-2-propenoic acid, N-bromosuccinimide, Ph_3P, pyridine, CH_2Cl_2; (e) TFA, CH_2Cl_2, H_2O

The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention. In the Examples, mass spectra were performed upon a VG Zab mass spectrometer using fast atom bombardment, unless otherwise indicated.

EXAMPLES

Preparation 1

Preparation of 4-Methoxy-3-[2-(2,2,6,6-tetramethylpiperidin-1-yl)ethoxy]aniline

a) 4-methoxy-1-nitro-3-[2-(2,2,6,6-tetramethylpiperidin-1-yl)ethoxy]benzene

A solution of 3-(2-bromoethoxy)-4-methoxy-1-nitrobenzene (Mutai et al., *Tetrahedron*, **1984**, 40, 755) (3 g, 11 mmol) and 2,2,6,6-tetramethylpiperidine (23 g, 163 mmol) in dimethylformamide (60 mL) containing sodium iodide (1.65 g, 11 mmol) and potassium carbonate (2.4 g, 17 mmol) was stirred and heated to 110°C for 16 h. The mixture was cooled, diluted with dichloromethane to 350 mL, filtered, and the filtrate was concentrated *in vacuo*. The residue was partitioned between ethyl acetate (350 mL) and water (40 mL), the organic phase was washed with water (3 x 40 mL), dried (Na_2SO_4), concentrated *in vacuo*, and the residue was purified by flash chromatography (silica gel, dichloromethane followed by 2% methanol/dichloromethane-0.1% ammonia). Fractions containing the title compound were combined, concentrated *in vacuo*, and the residue was purified by flash chromatography (silica gel, 50% ethyl acetate/hexane) to give the title compound. MS(ES) m/e 337 $[M+H]^+$.

b) 4-methoxy-3-[2-(2,2,6,6-tetramethylpiperidin-1-yl)ethoxy]aniline

A mixture of the compound of Preparation 1(a) (0.57 g, 1.7 mmol), 5% palladium-on-carbon (0.40 g), and methanol (100 mL) was shaken in a hydrogen atmosphere (50 psi) for 3 h, degassed, filtered, and the filtrate was concentrated *in vacuo* to give the title compound. MS(ES) m/e 307 $[M+H]^+$.

Preparation 2

Preparation of 4-Methoxy-3-[2-(4-hydroxy-2,2,6,6-tetramethylpiperidin-1-yl)ethoxy]aniline Following the procedure of Preparation 1(a)-(b), except substituting 4-hydroxy-2,2,6,6-tetramethylpiperidine for 2,2,6,6-tetramethylpiperdine, gave the title compound.

Preparation 3

Preparation of 6-Amino-4-[2-[bis(1-methylethyl)amino]ethyl]-2H-1,4-benzoxazin-3(4H)-one

a) 4-[2-[bis(1-methylethyl)amino]ethyl]-6-nitro-2H-1,4-benzoxazin-3(4H)-one

Sodium hydride (0.97 g of 60% dispersion in mineral oil, 24 mmol) was added portionwise to a suspension of 6-nitro-2H-1,4-benzoxazine-3(4H)-one (*J. Med. Chem.* **1989**, 32, 1627-1630)(4.3 g, 22 mmol) in tetrahydrofuran (100 mL) at RT resulting in a yellow heterogeneous mixture. 2-

(Diisopropylamino)ethyl chloride hydrochloride was dissolved in water (80 mL) and then sodium carbonate was added until the solution was saturated. The free amine was extracted with toluene (2 × 35 mL) and the toluene extracts were dried ($MgSO_4$) and added dropwise to the above sodium salt. The resultant mixture was heated at reflux for 4 h, cooled, quenched with water (100 mL), and extracted with ethyl acetate (2 × 100 mL). The organic layers were combined, washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was triturated with hexanes to give 4.4 g (62 %) of the title compound as an off-white powder. MS(ES) m/e 322.1 $[M+H]^+$.

b) 6-amino-4-[2-[bis(1-methylethyl)amino]ethyl]-2H-1,4-benzoxazin-3(4H)-one

5% Palladium-on-carbon (0.8 g) was added to a solution of the compound of Preparation 3(a) (1.0 g, 3.1 mmol) and ethanol (25 mL). The resultant mixture was hydrogenated at 50 psi for 1 h. The mixture was then filtered through a pad of Celite® and concentrated *in vacuo* to afford 0.55 g (61%) of title compound as a white crystalline solid. MS(ES) m/e 292.1 $[M+H]^+$.

Preparation 4

Preparation of 6-Amino-2,3-dihydro-N,N-bis(1-methylethyl)-4H-1,4-benzoxazine-4-ethanamine

a) 2,3-dihydro-N,N-[bis(1-methylethyl)-6-nitro-4H-1,4-benzoxazine-4-ethanamine

Boron trifluoride etherate (3.2 mL, 3.5 g, 25 mmol) was added slowly to a suspension of sodium borohydride (0.71 g, 14 mmol) in tetrahydrofuran (45 mL). The heterogeneous mixture was stirred at RT for 1 h, treated with a solution of the compound of Preparation 3(a) (2.0 g, 6.2 mmol) in tetrahydrofuran (30 mL), and the mixture heated at reflux for 2.5 h. The mixture was cooled to RT, excess reagent was quenched with saturated sodium bicarbonate, and the mixture was concentrated *in vacuo*. The residue was dissolved in ethanol (20 mL) and 3N hydrochloric acid (20 mL), and heated at reflux for 1 h. The mixture was made basic with 10% sodium carbonate and extracted with ethyl acetate (2 × 100 mL). The organic layers were combined, washed with brine, dried ($MgSO_4$), and concentrated to give the title compound as a yellow oil (1.7 g, 89%). MS(ES) m/e 308.1 $[M+H]^+$.

b) 6-amino-2,3-dihydro-N,N-bis(1-methylethyl)-4H-1,4-benzoxazine-4-ethanamine

Following the procedure of Preparation 3(b), except substituting the compound of Preparation 4(a) for the compound of Preparation 3(a), gave the title compound.

Preparation 5

Preparation of 5-Amino-3-[2-[Bis(1-methylethyl)amino]ethyl]-2(3H)-benzoxazolone Following the procedure of Preparation 3(a)-(b), except substituting 5-nitro-2(3H)-benzoxazolone (WO 95/32967) for 6-nitro-2H-1,4-benzoxazin-3(4H)-one, gave the title compound.

Preparation 6

Preparation of 7-Amino-3,4-dihydro-N,N-bis(1-methylethyl)-1(2H)-quinolineethanamine

a) 3,4-dihydro-N,N-bis(1-methylethyl)-7-nitro-1(2H)-quinolineethanamine

Sodium carbonate (2.9 g, 27 mmol) was added to a mixture of 7-nitro-1,2,3,4-tetrahydroquinoline (United States Patent 5696133) (1.2 g, 6.7 mmol), 2-(diisopropylamino)ethyl chloride hydrochloride (4.0 g, 20 mmol) and ethanol (25 mL). The mixture was heated at reflux for 3 h, filtered, and concentrated *in vacuo*. The crude product was purified by chromatography (silica gel, dichloromethane followed by 5% methanol/dichloromethane) to afford 1.4 g (68%) of the title compound as a yellow oil. MS(ES) m/e 306.1 $[M+H]^+$.

b) 7-amino-3,4-dihydro-N,N-bis(1-methylethyl)-1(2H)-quinolineethanamine

Following the procedure of Preparation 3(b) except substituting the compound of Preparation 6(a) for the compound of Preparation 3(a), gave the title compound.

Preparation 7

Preparation of 6-Amino-2,3-dihydro-N,N-bis(1-methylethyl)-1H-indole-1-ethanamine Following the procedure of Preparation 6(a)-(b), except substituting 2,3-dihydro-6-nitro-1H-indole for 7-nitro-1,2,3,4-tetrahydroquinoline, gave the title compound.

Preparation 8

Preparation of N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H),4'-piperidin]-5-amine

a) 5- and 7-nitrospiro[benzofuran-3(2H),4'-piperidine]

A solution of 1'-methyl-5- and 7-nitrospiro[benzofuran-3(2H),4'-piperidine] (WO 96/11934) (3 g, 12 mmol) and diisopropylethylamine (2.5 g,

19 mmol) in 1,2-dichloroethane (80 mL) was treated with 1-chloroethyl chloroformate (2.3 g, 16 mmol) at RT, stirred for 1 h, and heated to reflux for 20 min. The mixture was cooled, concentrated *in vacuo*, and the residue was dissolved in methanol, heated to reflux for 2 h, concentrated *in vacuo*, and the residue was partitioned between dichloromethane (250 mL) and 5% sodium bicarbonate (50 mL). The organic phase was washed with 5% sodium bicarbonate (50 mL) and the combined aqueous phase was extracted with dichloromethane (2 X 50 mL). The combined organic phase was dried (Na_2SO_4) and concentrated to afford the title compound (2. 65 g).

b) 1'-(tert-butoxycarbonyl)-5-nitrospiro[benzofuran-3(2H),4'-piperidine]

A solution of the compound of Preparation 8(a)(2.65 g, 1.13 mmol) in tetrahydrofuran (300 mL) was treated with di-tert-butyl dicarbonate (2.6 g, 12 mmol) and stirred at RT for 16 h. The mixture was concentrated *in vacuo* and the residue was crystallized from methanol to afford the title compound (2.1 g).

c) 5-nitrospiro[benzofuran-3(2H),4'-piperidine]

A solution of the compound of Preparation 8(b)(2.1 g, 6.3 mmol) in dichloromethane (50 mL) and trifluoroacetic acid (10 mL) was kept at RT for 5 h, concentrated *in vacuo*, and the residue was partitioned between dichloromethane (300 mL) and 5% sodium bicarbonate. The organic phase was washed with 5% sodium bicarbonate and the combined aqueous washes were extracted with dichloromethane. The combined organic phase was dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound (1.45 g).

MS(ES) m/e 235.1 $[+H]^+$.

d) 1'-(1-methylethyl)-5-nitrospiro[benzofuran-3(2H),4'-piperidine]

A mixture of the compound of Preparation 8(c) (1.45 g, 6.2 mmol), powdered potassium carbonate (0.86 g, 6.2 mmol) and dimethylformamide (50 mL) containing 2-iodopropane (1.1 g, 6.4 mmol) was stirred and heated to 50°C for 4 h, treated with 2-iodopropane (0.17 g, 1 mmol) at 50°C for 90 min, and treated with 2-iodopropane (0.1 g, 1 mmol) at 50°C for 2 h. The mixture was concentrated *in vacuo* and the residue was partitioned between ethyl acetate (200 mL) and water (20 mL). The organic phase was washed, dried ($MgSO_4$), concentrated *in vacuo*, and the residue was chromatographed (silica gel, 5% methanol/dichloromethane) to give the title compound (0.85 g).

e) N-[1'-(1-methylethyl)spiro[benzofuran-3(2H),4'-piperidin]-5-amine

A solution of the compound of Preparation 8(d) (0.78 g, 2.8 mmol) in methanol (250 mL) containing 10% palladium-on-carbon (0.375 g) was shaken in a hydrogen atmosphere (40 psi) for 40 min, filtered, and concentrated *in vacuo* to afford the title compound (0.6 g).

Preparation 9

Preparation of 3-[2-Acetoxy-3-(diisopropylamino)propoxy]-4-methoxyaniline

a) 4-methoxy-3-(oxiranyl)methoxy-1-nitrobenzene

A solution of 3-chloroperbenzoic acid (11 mmol) in dichloromethane (50 mL) was added dropwise to a solution of 1-methoxy-4-nitro-2-(2-propenyloxy)benzene (Molina et al., *Tetrahedron Lett.*, **1992**, 33, 2387-90) (2 g, 9.6 mmol) in dichloromethane (50 mL) and stirred at RT for 6 d. The mixture was washed with 5% sodium sulfite (35 mL) and then with 5% sodium bicarbonate. The organic phase was dried ($MgSO_4$), concentrated *in vacuo*, and the residue was recrystallized from ethanol (50 mL) to give the title compound (1 g) as a yellow solid.

b) 3-[3-diisopropylamino-2-(hydroxy)propoxy]-4-methoxy-1-nitrobenzene

A mixture of the compound of Preparation 9(a)(1 g, 4.4 mmol) and diisopropylamine (5.7 g, 44 mmol) in ethanol (50 mL) was heated to 50°C for 2 h, cooled, kept at RT for 16 h, heated to 50°C for 6 h, cooled, and concentrated *in vacuo* to give the title compound as a yellow oil (1.4 g). MS(ES) m/e 327.0 $[M+H]^+$.

c) 3-[2-acetoxy-3-(diisopropylamino)propoxy]-4-methoxy-1-nitrobenzene

A solution of the compound of Preparation 9(b)(1.4 g, 4.2 mmol) and diisopropylethylamine (0.57 g, 4.4 mmol) in dichloromethane (50 mL) was treated with acetyl chloride (0.35 g, 4.4 mmol) at RT and stirred for 16 h. The mixture was washed with 5% sodium carbonate, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was chromatographed (silica gel, 3% methanol/dichloromethane) and fractions containing the title compound were combined, concentrated *in vacuo* and rechromatographed (silica gel, 1% methanol/dichloromethane) to give the title compound (0.9 g). MS(ES) m/e 369.0 $[M+H]^+$.

d) 3-[2-acetoxy-3-(diisopropylamino)proxy]-4-methoxyaniline

A solution of the compound of Preparation 9(c)(0.27 g, 0.73 mmol) in methanol(50 mL) containing 10% palladium-on-carbon (0.1 g) was shaken in a hydrogen atmosphere (40 psi) at RT for 1 h. The mixture was filtered and

concentrated *in vacuo* to give the title compound. MS(ES) m/e 339.0 $[M+H]^+$.

Preparation 10

Preparation of (S)-2-[(2-methoxy-5-nitrophenoxy)methyl]pyrrolidine

(S)-1-(tert-Butoxycarbonyl)-2-pyrrolidinemethanol (28.2 g, 0.14 mol) and 2-methoxy-5-nitrophenol (24.1 g, 0.14 mol) were stirred in anhydrous tetrahydrofuran (1.5 L). Triphenylphosphine (36.7 g, 0.14 mol) was added and the mixture was stirred, cooled in an ice bath to 10°C, and diethyl azodicarboxylate (24.4 g, 0.14 mol) was added over 30 min while the reaction temperature was maintained below 25°C. The mixture was then allowed to stand at RT for 16 h, concentrated *in vacuo*, the residue dissolved in dichloromethane (1500 ml), and washed with 10% aqueous sodium hydroxide and water. The organic phase was dried (Na_2SO_4), filtered, and the filtrate was treated with trifluoroacetic acid (100 mL) and allowed to stand at RT for 16 h. The mixture was concentrated *in vacuo* and the residue was dissolved in diethyl ether (1.5 L). The ether solution was extracted thoroughly with 10% hydrochloric acid, and the aqueous phase was washed with ether and then basified with 40% aqueous sodium hydroxide. The product was extracted into ether, and the ether solution was washed with water, dried (Na_2SO_4), and concentrated *in vacuo* to afford the title compound (24.48g, 70% yield) as a yellow solid. MS(ES) m/e 253 $[M+H]^+$.

Example 1

Preparation of N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3,4-dichlorophenyl)-2-propenamide

A solution of 3,4-dichlorocinnamoyl chloride (0.2 g, 0.85 mmol), prepared from 3,4-dichlorocinnamic acid and thionyl chloride, in dichloromethane (10 mL) was added in one portion to a solution of 3-[2-(diisopropylamino)ethoxy]-4-methoxyaniline (WO 95/15954)(0.23 g, 0.85 mmol) and diisopropylethylamine (0.11 g, 0.85 mmol) in dichloromethane (10 mL), and the mixture was stirred at RT for 16 h. The mixture was diluted with dichloromethane (50 mL), washed with 5% aqueous sodium carbonate, dried (Na_2SO_4), concentrated *in vacuo*, and the residue was purified by flash chromatography (silica gel, 5% methanol/dichloromethane-0.1% ammonia) to afford the title compound (250 mg, 63%). MS(ES) m/e 465.3 $[M+H]^+$.

Examples 2-3

Preparation of N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-phenyl-2-propenamide and N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2-naphthalenyl)-2-propenamide

Following the procedure of Example 1, except substituting cinnamic acid and 3-(2-naphthalenyl)-2-propenoic acid for 3,4-dichlorocinnamic acid, gave the title compounds:

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-phenylpropenamide: MS(ES) m/e 397.3 $[M+H]^+$; and

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2-naphthalenyl)-2-propenamide: MS(ES) m/e 446.9 $[M+H]^+$.

Example 4

Preparation of (E)-N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-[4-chloro-3-(trifluoromethyl)phenyl]-2-propenamide

Following the procedure of Example 1, except substituting 4-chloro-3-(trifluoromethyl)cinnamic acid for 3,4-dichlorocinnamic acid and substituting triethylamine for diisopropylethylamine, gave the title compound. MS(ES) m/e 498.7, 500.7 $[M+H]^+$.

Example 5

Preparation of (E)-N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3-chlorophenyl)-2-propenamide

A solution of 3-chlorocinnamic acid (0.18 g, 1 mmol), 3-[2-(diisopropylamino)ethoxy]-4-methoxyaniline (WO 95/15954)(0.27 g, 1 mmol), and BOP reagent (0.44 g, 1 mmol) in acetonitrile (20 mL) was treated with triethylamine (0.22 g, 2.2 mmol) and stirred at RT for 16 h. The mixture was treated with brine (50 mL) and extracted with ethyl acetate. The combined organic phase was washed with 5% sodium carbonate and with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed (silica gel, 5% methanol/dichloromethane) to give the title compound (0.2 g). MS(ES) m/e 431.1 $[M+H]^+$.

Examples 6-12

Following the procedure of Example 5, except substituting 3-(5-indolyl)-2-propenoic acid, 3-(6-indolyl)-2-propenoic acid, •,•-dimethylcinnamic acid, •-(acetylamino)-3,4-dichlorocinnamic acid, 3-(5,6,7,8-tetrahydronaphth-2-yl)-2-propenoic acid, 4-chloro-3-methylcinnamic acid, and 3,4-dichloro-•-methylcinnamic acid for 3-chlorocinnamic acid, gave the following compounds:

(E)-N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(5-indolyl)-2-propenamide: MS(ES) m/e 435.9 $[M+H]^+$;

(E)-N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl)-3-(6-indolyl)-2-propenamide: MS(ES) m/e 436.1 $[M+H]^+$;

(E)-•••-dimethyl-N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-phenyl-2-propenamide: MS(ES) m/e 425.0 $[M+H]^+$;
(Z)-N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl)-•-(acetylamino)-3-(3,4-dichlorophenyl)-2-propenamide: MS(ES) m/e 521.7, 523.6 $[M+H]^+$;
(E)-N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(5,6,7,8-tetrahydronaphth-2-yl)-2-propenamide trifluoroacetate salt: MS(ES) m/e 450.5 $[M+H]^+$;
(E)-N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(4-chloro-3-methylphenyl)-2-propenamide: MS(ES) m/e 444.8, 446.8 $[M+H]^+$; and
(E)-N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3,4-dichlorophenyl)-•-methyl-2-propenamide: MS(ES) m/e 478.7, 480.7 $[M+H]^+$.

Examples 13-15

Preparation of N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxypheny]-3-(4-fluorophenyl)-2-propenamide; (E)-N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3,5-dichlorophenyl)-2-propenamide trifluoroacetate; and (E)-N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-[4-(trifluoromethyl)phenyl]-2-propenamide

Following the procedure of Example 5, except substituting 4-fluorocinnamic acid, 3,5-dichlorocinnamic acid, and 4-(trifluoromethyl)cinnamic acid for 3-chlorocinnamic acid, gave the title compounds:
N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxypheny]-3-(4-fluorophenyl)-2-propenamide: MS(ES) m/e 414.9 $[M+H]^+$;
(E)-N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3,5-dichlorophenyl)-2-propenamide trifluoroacetate: MS(ES) m/e 466.8 $[M+H]^+$; and
(E)-N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-[(4-trifluoromethyl)phenyl]-2-propenamide: MS(ES) m/e 464.8 $[M+H]^+$.

Example 16

Preparation of N-[3-[2-(2,2,6,6-tetramethylpiperidin-1-yl)ethoxy]-4-methoxy-phenyl]-3-(3,4-dichlorophenyl)-2-propenamide

Following the procedure of Example 1, except substituting the compound of Preparation 1(b) for 3-[2-(diisopropylamino)ethoxy]-4-methoxyaniline, gave the title compound. MS(ES) m/e 505.0 $[M+H]^+$.

Example 17

Preparation of N-[3-[2-(4-Hydroxy-2,2,6,6-tetramethylpiperidin-1-yl)ethoxy]-4-methoxyphenyl]-3-(3,4-dichlorophenyl)-2-propenamide

Following the procedure of Example 16, except substituting the compound of Preparation 2 for the compound of Preparation 1(b), gave the title compound. MS(ES) m/e 521.1, 523.1 $[M+H]^+$.

Examples 18-22

Preparation of N-[4-[2-[Bis(1-methylethyl)amino]ethyl]-3,4-dihydro-3-oxo-2H-1,4-benzoxazin-6-yl]-3-(3,4-dichlorophenyl)-2-propenamide; N-[4-[2-[Bis(1-methylethyl)amino]ethyl]-3,4-dihydro-2H-1,4-benzoxazin-6-yl]-3-(3,4-dichlorophenyhl-2-propenamide; N-[3-[2-[Bis(1-methylethyl)amino]ethyl]-2-oxo-(3H)-benzoxazol-5-yl]-3-(3,4-dichlorophenyl)-2-propenamide; N-[2,3-Dihydro-1-[2-[bis(1-methylethyl)amino]ethyl]-1H-indol-6-yl]-3-(3,4-dichlorophenyl)-2-propenamide; and N-[1-[2-[Bis(1-methylethyl)amino]ethyl]-1,2,3,4-tetrahydroquinol-7-yl]-3-(3,4-dichlorophenyl)-2-propenamide

Following the procedure of Example 1, except substituting the compounds of Preparations 3-7 for 3-[2-(diisopropylamino)ethoxy]-4-methoxyaniline, gave the title compounds:

N-[4-[2-[bis(1-methylethyl)amino]ethyl]-3,4-dihydro-3-oxo-2H-1,4-benzoxazin-6-yl]-3-(3,4-dichlorophenyl)-2-propenamide: MS(ES) m/e 490.0, 491.9 $[M+H]^+$;

N-[4-[2-[bis(1-methylethyl)amino]ethyl]-3,4-dihydro-2H-1,4-benzoxazin-6-yl]-3-(3,4-dichlorophenyhl-2-propenamide: MS(ES) m/e 476.0, 477.9 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethyl]-2-oxo-(3H)-benzoxazol-5-yl]-3-(3,4-dichlorophenyl)-2-propenamide: MS(ES) m/e 475.9, 477.9 $[M+H]^+$;

N-[2,3-dihydro-1-[2-[bis(1-methylethyl)amino]ethyl]-1H-indol-6-yl]-3-(3,4-dichlorophenyl)-2-propenamide: MS(ES) m/e 459.9, 461.9 $[M+H]^+$; and

N-[1-[2-[bis(1-methylethyl)amino]ethyl]-1,2,3,4-tetrahydroquinol-7-yl]-3-(3,4-dichlorophenyl)-2-propenamide: MS(ES) m/e 474.1, 476.1 $[M+H]^+$.

Example 23

Preparation of N-(1'-Methylspiro[benzofuran-3(2H),4'-piperidin]-5-yl)-3-(3,4-dichlorophenyl)-2-propenamide Following the procedure of Example 1, except substituting 1'-methyl-5-nitrospiro[benzofuran-3(2H),4'-piperidine] (WO 96/11934) for 3-[2-(diisopropylamino)ethoxy]-4-methoxyaniline, gave the title compound: MS(ES) m/e 418.4 $[M+H]^+$.

Example 24

Preparation of N-(Spiro[benzofuran-3(2H),4'-piperidin]-5-yl)-3-(3,4-dichlorophenyl)-2-propenamide

A solution of the compound of Example 23(0.28 g, 0.67 mmol) and diisopropylethylamine (0.13 g, 1 mmol) in 1,2-dichloroethane (15 mL) was treated with 1-chloroethyl chloroformate (0.12 g, 0.86 mmol), stirred for 1 h at RT, and heated to reflux for 20 min. The mixture was cooled, concentrated *in vacuo*, and the residue was dissolved in methanol (25 mL), heated to reflux for 2 h, and stirred at RT for 16 h. The mixture was cooled, concentrated *in vacuo*, and the residue was dissolved in dichloromethane (100 mL) and washed with 5% sodium carbonate. The organic phase was dried ($MgSO_4$), concentrated *in vacuo*, treated with dichloromethane, and concentrated *in vacuo* several times to give the title compound. MS(ES) m/e 404 $[M+H]^+$.

Example 25

Preparation of N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H)4'-piperidin]-5-yl]-3-(3,4-dichlorophenyl)-2-propenamide

A solution of the compound of Example 24 (0.15 g, 0.37 mmol) in dimethylformamide containing 2-iodopropane (65 mg, 0.38 mmol) and powdered potassium carbonate (56 mg, 0.4 mmol) was heated to 50°C for 15 h, cooled, and concentrated *in vacuo*. The residue was partitioned between ethyl acetate (120 mL) and water (10 mL), and the organic phase was washed with water and with brine, dried (Mg SO_4), and concentrated *in vacuo*. The residue was chromatographed (silica gel, 5% methanol/dichloromethane) to give the title compound. MS(ES) m/e 446.9 $[M+H]^+$.

Example 26

Preparation of N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H)4'-piperidin]-5-yl]-3-(3,5-dichlorophenyl)-2-propenamide Following the procedure of Example 5, except substituting 3,5-dichlorocinnamic acid for 3-chlorocinnamic acid and the compound of Preparation 8(e) for 3-[2-(diisopropylamino)ethoxy]-4-methoxyaniline, gave the title compound. MS(ES) m/e 445.0 $[M+H]^+$.

Example 27

Preparation of N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3,4-dichlorophenyl)-2-propenamide Following the procedure of Example 1, except substituting 3-[3-(diisopropylamino)propyl]-4-methoxyaniline (WO 99/01127) for 3-[2-(diisopropylamino)ethoxy]-4-methoxyaniline, gave the title compound. MS(ES) m/e 462.9 $[M+H]^+$.

Example 28

Preparation of N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3,4-dichlorophenyl)-2-propenamide

Following the procedure of Example 1, except substituting 3-[3-(diisopropylamino)propoxy]-4-methoxyaniline (WO 99/01127) for 3-[2-(diisopropylamino)ethoxy]-4-methoxyaniline, gave the title compound. MS(ES) m/e 480.7 $[M+H]^+$.

Example 29

Preparation of N-[3-[2-Acetoxy-3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3,4-dichlorophenyl)-2-propenamide

Following the procedure of Example 1, except substituting the compound of Preparation 9(d) for 3-[2-(diisopropylamino)ethoxy]-4-methoxyaniline, gave the title compound. MS(ES) m/e 538.9 $[M+H]^+$.

Example 30

Preparation of N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(4-chlorophenyl)-2-propenamide

a) [3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyaniline/(4-formyl-3,5-dimethoxy-phenoxy)-Merrifield resin adduct

A mixture of 4-formyl-3,5-dimethoxy-phenoxy-Merrifield resin (Boojamra et al., *J. Org. Chem.* **1995**, 60, 5742-3), 3-[3-(diisopropylamino)propyl]-4-methoxyaniline (WO 99/01127), and sodium triacetoxyborohydride in dimethylformamide containing 1% acetic acid was shaken to afford the title adduct.

b) N-[3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(4-chlorophenyl)-2-propenamide/(4-formyl-3,5-dimethoxy-phenoxy)-Merrifield resin adduct

The resin of Example 30(a) was placed in an Irori MicroKan and treated with a ten-fold molar excess of an equimolar mixture of 4-chlorocinnamic acid, N-bromosuccinimide, and triphenylphosphine in dichloromethane, followed by addition of a ten-fold excess of pyridine. The mixture was gently agitated for 48 h after which the resin was washed three-times, sequentially with dimethylformamide, dichloromethane, and methanol to afford the title adduct.

c) N-[3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(4-chlorophenyl)-2-propenamide

The resin of Example 30(b) was stirred in a mixture of trifluoroacetic acid:dichloromethane:water (50:48:2), filtered, and the filtrate concentrated *in vacuo* to afford the title compound. MS(ES) m/e 429.0 $[M+H]^+$.

Examples 31-62

Following the procedure of Example 30(a)-(c), except substituting 3-[2-(diisopropylamino)ethoxy]-4-methoxyaniline (WO 95/15954), 3-[2-(N-cyclohexyl-N-isopropylamino)ethoxy]-4-methoxyaniline (WO 99/01127), and 3-[2-(cis-2,6-dimethylpiperidin-1-yl)ethoxy]-4-methoxyaniline (WO 99/01127) for 3-[3-(diisopropylamino)propyl]-4-methoxyaniline, and using 3-chlorocinnamic acid, 3,4-(methylenedioxy)cinnamic acid, 3,4-difluorocinnamic acid, and 3-(2-naphthalenyl)-2-propenoic acid, in addition to 4-chlorocinnamic acid, gave the title compounds:

N-[3-[2-(cis-2,6-dimethylpiperidin-1-yl)ethoxy]-4-methoxyphenyl]-3-(3-chlorophenyl)-2-propenamide: MS(ES) m/e 443.0 $[M+H]^+$;

N-[3-[2-(N-cyclohexyl-N-isopropylamino)ethoxy]-4-methoxyphenyl]-3-(3-chlorophenyl)-2-propenamide: MS(ES) m/e 471.0 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(4-chlorophenyl)-2-propenamide: MS(ES) m/e 431.0$[M+H]^+$;

N-[3-[2-(cis-2,6-dimethylpiperidin-1-yl)ethoxy]-4-methoxyphenyl]-3-(4-chlorophenyl)-2-propenamide: MS(ES) m/e 442.9$[M+H]^+$;

N-[3-[2-(N-cyclohexyl-N-isopropylamino)ethoxy]-4-methoxyphenyl]-3-(4-chlorophenyl)-2-propenamide: MS(ES) m/e 470.9 $[M+H]^+$;

N-[3-[2-(N-cyclohexyl-N-isopropylamino)ethoxy]-4-methoxyphenyl]-3-[(3,4-methylenedioxy)phenyl]-2-propenamide: MS(ES) m/e 481.0 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3,4-difluorophenyl)-2-propenamide: MS(ES) m/e 432.9 $[M+H]^+$;

N-[3-[2-(cis-2,6-dimethylpiperidin-1-yl)ethoxy]-4-methoxyphenyl]-3-(3,4-difluorophenyl)-2-propenamide: MS(ES) m/e 444.9 $[M+H]^+$;

N-[3-[2-(N-cyclohexyl-N-isopropylamino)ethoxy]-4-methoxyphenyl]-3-(3,4-difluorophenyl)-2-propenamide: MS(ES) m/e 473.0 $[M+H]^+$;

N-[3-[2-(N-cyclohexyl-N-isopropylamino)ethoxy]-4-methoxyphenyl]-3-(2-naphthalenyl)-2-propenamide: MS(ES) m/e 487.4 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-[3-(trifluoromethyl)phenyl]-2-propenamide: MS(ES) m/e 465.2 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2-chlorophenyl)-2-propenamide: MS(ES) m/e 431.2 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2,4-dichlorophenyl)-2-propenamide: MS(ES) m/e 465.2 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2,6-dichlorophenyl)-2-propenamide: MS(ES) m/e 465.2 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3,5-difluorophenyl)-2-propenamide: MS(ES) m/e 433.2 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2,5-difluorophenyl)-2-propenamide: MS(ES) m/e 433.2 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2,4-difluorophenyl)-2-propenamide: MS(ES) m/e 433.2 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3-fluorophenyl)-2-propenamide: MS(ES) m/e 415.2 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2-chloro-6-fluorophenyl)-2-propenamide: MS(ES) m/e 449.2 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(4-bromo-2-fluorophenyl)-2-propenamide: MS(ES) m/e 493.1 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(4-chloro-2-fluorophenyl)-2-propenamide: MS(ES) m/e 449.2 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2-chloro-4-fluorophenyl)-2-propenamide: MS(ES) m/e 449.2 $[M+H]^+$

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2,6-difluorophenyl)-2-propenamide: MS(ES) m/e 433.2 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(4-bromophenyl)-2-propenamide: MS(ES) m/e 475.2 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(4-chloro-3-nitrophenyl)-2-propenamide: MS(ES) m/e 476.2 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-[4-(1-methylethyl)phenyl]-2-propenamide: MS(ES) m/e 439.3 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(5-bromo-2-methoxyphenyl)-2-propenamide: MS(ES) m/e 505.2 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-([1,1'-biphenyl]-4-yl)-2-propenamide: MS(ES) m/e 473.3 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3-bromo-4-fluorophenyl)-2-propenamide: MS(ES) m/e 493.1 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3,4-dimethylphenyl)-2-propenamide: MS(ES) m/e 425.3 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(4-cyanophenyl)-2-propenamide: MS(ES) m/e 422.2 $[M+H]^+$; and

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2-fluoro-3-phenyl-2-propenamide: MS(ES) m/e 415.2 $[M+H]^+$.

Examples 63-90

Following the procedure of Example 30(b)-(c), except substituting 3,4-difluorocinnamic acid, 3,4-dichlorocinnamic acid, 3-chlorocinnamic acid, 3,4-(methylenedioxy)cinnamic acid, and 3-(2-naphthalenyl)-2-propenoic acid for 4-chlorocinnamic acid, gave the title compounds:

N-[3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3,4-difluorophenyl)-2-propenamide: MS(ES) m/e 431.2 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3,4-dichlorophenyl)-2-propenamide: MS(ES) m/e 462.9 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3-chlorophenyl)-2-propenamide: MS(ES) m/e 428.9$[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-[(3,4-methylenedioxy)phenyl]-2-propenamide: MS(ES) m/e 438.9$[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(2-naphthalenyl)-2-propenamide: MS(ES) m/e 445.4 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-[4-(trifluoromethyl)phenyl]-2-propenamide: MS(ES) m/e 463.3 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-[3-(trifluoromethyl)phenyl]-2-propenamide: MS(ES) m/e 463.3 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(2-chlorophenyl)-2-propenamide: MS(ES) m/e 429.2 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(2,4-dichlorophenyl)-2-propenamide: MS(ES) m/e 463.2 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(2,6-dichlorophenyl)-2-propenamide: MS(ES) m/e 463.2 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3,5-difluorophenyl)-2-propenamide: MS(ES) m/e 431.3 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(2,5-difluorophenyl)-2-propenamide: MS(ES) m/e 431.3 $[M+H]^+$;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(2,4-difluorophenyl)-2-propenamide: MS(ES) m/e 431.3 $[M+H]^+$;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3-fluorophenyl)-2-propenamide: MS(ES) m/e 413.3 $[M+H]^+$;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(2-chloro-6-fluorophenyl)-2-propenamide: MS(ES) m/e 447.2 $[M+H]^+$;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(4-bromo-2-fluorophenyl)-2-propenamide: MS(ES) m/e 491.2 $[M+H]^+$;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(4-chloro-2-fluorophenyl)-2-propenamide: MS(ES) m/e 447.2 $[M+H]^+$;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(2-chloro-4-fluorophenyl)-2-propenamide: MS(ES) m/e 447.2 $[M+H]^+$;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(2,6-difluorophenyl)-2-propenamide: MS(ES) m/e 431.3 $[M+H]^+$;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(4-bromophenyl)-2-propenamide: MS(ES) m/e 473.2 $[M+H]^+$;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(4-chloro-3-nitrophenyl)-2-propenamide: MS(ES) m/e 474.2 $[M+H]^+$;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-[4-(1-methylethyl)phenyl]-2-propenamide: MS(ES) m/e 437.3 $[M+H]^+$;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(5-bromo-2-methoxyphenyl)-2-propenamide: MS(ES) m/e 503.2 $[M+H]^+$;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3-bromo-4-fluorophenyl)-2-propenamide: MS(ES) m/e 491.2 $[M+H]^+$;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3,5-dichlorophenyl)-2-propenamide: MS(ES) m/e 463.2 $[M+H]^+$;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3,4-dimethylphenyl)-2-propenamide: MS(ES) m/e 423.3 $[M+H]^+$

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(4-cyanophenyl)-2-propenamide: MS(ES) m/e 420.3 $[M+H]^+$; and

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-2-fluoro-3-phenyl-2-propenamide: MS(ES) m/e 413.3 $[M+H]^+$.

Examples 91-117

Following the procedure of Example 30(a)-(c), except substituting 3-[3-(diisopropylamino)propoxy]-4-methoxyaniline (WO 99.01127) for 3-[3-(diisopropylamino)propyl]-4-methoxyaniline and using 3-chlorocinnamic acid, 3,4-(methylenedioxy)cinnamic acid, 3,4-difluorocinnamic acid, and 3-(2-naphthalenyl)-2-propenoic acid, in addition to 4-chlorocinnamic acid, gave the title compounds:

N-[3-[3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3-chlorophenyl)-2-propenamide: MS(ES) m/e 444.9 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(4-chlorophenyl)-2-propenamide: MS(ES) m/e 444.9 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-[(3,4-methylenedioxy)phenyl]-2-propenamide: MS(ES) m/e 454.9 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3,4-difluorophenyl)-2-propenamide: MS(ES) m/e 446.9 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2-naphthalenyl)-2-propenamide: MS(ES) m/e 461.6 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-[3-(trifluoromethyl)phenyl]-2-propenamide: MS(ES) m/e 479.3 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2-chlorophenyl)]-2-propenamide: MS(ES) m/e 445.2 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2,4-dichlorophenyl)]-2-propenamide: MS(ES) m/e 479.2 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2,6-dichlorophenyl)]-2-propenamide: MS(ES) m/e 479.2 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3,5-difluorophenyl)]-2-propenamide: MS(ES) m/e 447.2 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2,5-difluorophenyl)]-2-propenamide: MS(ES) m/e 447.2 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2,4-difluorophenyl)]-2-propenamide(SB-383258): MS(ES) m/e 447.2 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3-fluorophenyl)]-2-propenamide: MS(ES) m/e 429.3 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2-chloro-6-fluorophenyl)]-2-propenamide: MS(ES) m/e 463.2 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(4-bromo-2-fluorophenyl)]-2-propenamide: MS(ES) m/e 507.2 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(4-chloro-2-fluorophenyl)]-propenamide: MS(ES) m/e 463.2 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2-chloro-4-fluorophenyl)-2-propenamide: MS(ES) m/e 463.2 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2,6-difluorophenyl)]-2-propenamide: MS(ES) m/e 447.2 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(4-bromophenyl)]-2-propenamide: MS(ES) m/e 489.2 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-[4-(1-methylethyl)phenyl]-2-propenamide: MS(ES) m/e 453.3 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-([1,1'-biphenyl]-4-yl)-2-propenamide: MS(ES) m/e 487.3 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2,3-dihydro-1H-inden-5-yl)-2-propenamide: MS(ES) m/e 451.3 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3-bromo-4-fluorophenyl)]-2-propenamide: MS(ES) m/e 507.2 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3,5-dichlorophenyl)]-2-propenamide: MS(ES) m/e 479.2 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3,4-dimethylphenyl)-2-propenamide: MS(ES) m/e 439.3 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(4-cyanophenyl)]-2-propenamide: MS(ES) m/e 436.3 $[M+H]^+$; and

N-[3-[3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-2-fluoro-3-phenyl-2-propenamide: MS(ES) m/e 429.3 $[M+H]^+$.

Examples 118-120

Following the procedure of Example 30(a)-(c), except substituting 3-[2-(diisopropylamino)ethoxy]-4-methylaniline (WO 9901127) for 3-[3-(diisopropylamino)propyl]-4-methoxyaniline and substituting 3,4-(methylenedioxy)cinnamic acid, 3,4-difluorocinnamic acid, and 3-(2-naphthalenyl)-2-propenoic acid for 4-chlorocinnamic acid, gave the title compounds:

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methylphenyl]-3-[(3,4-methylenedioxy)phenyl]-2-propenamide: MS(ES) m/e 424.9 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methylphenyl]-3-(3,4-difluorophenyl)-2-propenamide: MS(ES) m/e 417.0 $[M+H]^+$; and

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methylphenyl]-3-(2-naphthalenyl)-2-propenamide: MS(ES) m/e 431.0 $[M+H]^+$.

Examples 121-135

Following the procedure of Example 30(a)-(c), except using 3-[2-(diisopropylamino)ethoxy]-4-methoxyaniline (WO 95/15954), 3-[2-(diisopropylamino)ethoxy]-4-methylaniline (WO 99/01127), 3-[2-(N-cyclohexyl-N-isopropylamino)ethoxy]-4-methoxyaniline (WO 99/01127), and 3-[2-(cis-2,6-dimethylpiperidin-1-yl)ethoxy]-4-methoxyaniline (WO 99/01127) in addition to 3-[3-(diisopropylamino)propyl]-4-methoxyaniline, and substituting 3-(3-thienyl)-2-propenoic acid, 3-(4-pyridinyl)-2-propenoic acid, 3-(3-furanyl)-2-propenoic acid, and

3-(2-thienyl)-2-propenoic acid for 4-chlorocinnamic acid, and using , afforded the title compounds:

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3-thienyl)-2-propenamide: MS(ES) m/e 403.0 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3-thienyl)-2-propenamide: MS(ES) m/e 401.0 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3-thienyl)-2-propenamide: MS(ES) m/e 417.0 $[M+H]^+$;

N-[3-[2-(cis-2,6-dimethylpiperidin-1-yl)ethoxy]-4-methoxyphenyl]-3-(3-thienyl)-2-propenamide: MS(ES) m/e 415.0 $[M+H]^+$;

N-[3-[2-(N-cyclohexyl-N-isopropylamino)ethoxy]-4-methoxyphenyl]-3-(3-thienyl)-2-propenamide: MS(ES) m/e 443.0 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methylphenyl]-3-(4-pyridinyl)-2-propenamide: MS(ES) m/e 382.0 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(4-pyridinyl)-2-propenamide: MS(ES) m/e 412 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3-furanyl)-2-propenamide: MS(ES) m/e 387.4 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methylphenyl]-3-(3-furanyl)-2-propenamide: MS(ES) m/e 371.0 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3-furanyl)-2-propenamide: MS(ES) m/e 385.0 $[M+H]^+$;

N-[3-[2-(cis-2,6-dimethylpiperidin-1-yl)ethoxy]-4-methoxyphenyl]-3-(3-furanyl)-2-propenamide: MS(ES) m/e 399.0 $[M+H]^+$;

N-[3-[2-(N-cyclohexyl-N-isopropylamino)ethoxy]-4-methoxyphenyl]-3-(3-furanyl)-2-propenamide: MS(ES) m/e 427.0 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(2-thienyl)-2-propenamide: MS(ES) m/e 401.0 $[M+H]^+$;

N-[3-[3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2-thienyl)-2-propenamide: MS(ES) m/e 417.0 $[M+H]^+$; and

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2-furanyl)-2-propenamide: MS(ES) m/e 387.1 $[M+H]^+$.

Example 136

Preparation of N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2-furanyl)-2-propenamide Following the procedure of Example 5, except substituting 3-(2-furanyl)-2-propenoic acid for 3-chlorocinnamic acid, afforded the title compound: MS(ES) m/e 387.1 $[M+H]^+$.

Examples 137-142

Following the procedure of Example 5, except substituting 3-(1H-indol-3-yl)-2-propenoic acid3-(1H-indol-2-yl)-2-propenoic acid, 3-(1-methyl-1H-indol-2-yl)-2-propenoic acid, 3-(benzo[b]thien-3-yl)-2-propenoic acid, 3-(2-benzofuranyl)-2-propenoic acid, and 3-(benzo[b]thien-2-yl)-2-propenoic acid for 3-chlorocinnamic acid, afforded the title compounds:

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(1H-indol-3-yl)-2-propenamide: MS(ES) m/e 435.9 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(1H-indol-2-yl)-2-propenamide: MS(ES) m/e 435.9 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(1-methyl-1H-indol-2-yl)-2-propenamide: MS(ES) m/e 439.9 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(benzo[b]thien-3-yl)-2-propenamide: MS(ES) m/e 452.3 $[M+H]^+$;

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2-benzofuranyl)-2-propenamide: MS(ES) m/e 436.9 $[M+H]^+$; and

N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(benzo[b]thien-2-yl)-2-propenamide: MS(ES) m/e 452.8 $[M+H]^+$.

Example 143

Preparation of N-[4-Methoxy-3-[(2S)-(1-methyl-2-pyrrolidinyl)methoxy]phenyl]-3-(3,4-dichlorophenyl)-2-propenamide

a) (S)-2-[(2-methoxy-5-nitrophenoxy)methyl]pyrrolidine/REM Resin Adduct

REM resin (264.2 g, 0.64 meq/g) was stirred with dimethylformamide (500 mL) under argon at RT for 30 min, and a solution of the compound of Preparation 10 (110.9 g 0.47 mol) in dimethylformamide (1 L) was added and the mixture stirred at RT for16 h. The resin was collected by filtration, washed with dimethylformamide, dichloromethane, and methanol, and dried *in vacuo* at RT to afford (272.8 g, 89% yield) of the title adduct with a theoretical loading of 0.55 meq/g.

b) (S)-2-[(2-methoxy-5-aminophenoxy)methyl]pyrrolidine/REM Resin Adduct

The adduct of Example 143(a) (268.1 g) was stirred with dimethylformamide (1 L) under argon at RT for 30 min and tin(II) chloride dihydrate (133.5 g 0.59 mol) in dimethylformamide (1 L) was added in one portion. The mixture was stirred at RT under argon for 48 h, the resin was collected by filtration, and washed with 10% v/v hydrochloric acid:dioxane 1:1, 10% diisopropylethylamine in dimethylformamide, 50:50 dioxane:water, dioxane, dichloromethane, and methanol. The product was dried *in vacuo* at RT to constant weight to give resin (261 g) with a theoretical loading 0.61 meq/g.

c) N-[4-Methoxy-3-[(2S)-(1-methyl-2-pyrrolidinyl)methoxy]phenyl]-3-(3,4-dichlorophenyl)-2-propenamide/REM Resin Adduct

A double Irori Kans was charged with the resin of Example 143(b) (100 mg) which was treated in dichloromethane with 3-(3,4-dichlorophenyl)-2-propenoic acid (12.3 mmol) followed by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.36 g) and 1-hydroxybenzotriazole hydrate (1.88 g). The mixture was stirred at RT for 30 min. The Kans were then stirred at RT for 16 h, and washed for approximately 5 min with each of the following 50:50 10% hydrochloric acid:dioxane, 10% diisopropylethylamine in dimethylformamide, 50:50 dioxane:water, dioxane, dichloromethane, and methanol. The Kans was dried *in vacuo* at RT for 16 h.

d) N-[4-Methoxy-3-[(2S)-(1-methyl-2-pyrrolidinyl)methoxy]phenyl]-3-(3,4-dichlorophenyl)-2-propenamide

The resin of Example 143(c) was washed for 30 min with dimethylformamide which was decanted, charged with dimethylformamide (100 mL), and treated with iodomethane (8.2 mmol). The mixture was stirred at RT for 48 h, the resin was removed and washed for 30 min with each of dimethylformamide, dioxane, dichloromethane, methanol, and diethyl ether. The resin was dried *in vacuo* at RT, removed from the Kans, and treated with 10% triethylamine in dimethylformamide (1 mL) for 16 h with added Amberlyst-A21. The mixture was filtered, treated with 1% triethylamine in dimethylformamide (1 mL), and agitated for 3 h. The solvent was transferred by filtration, and the residue was washed with dimethylformamide (1 mL) for 1 h. The solvent was concentrated *in vacuo* to afford the title compound.

Example 144

Preparation of N-[4-Methoxy-3-[(2S)-(1-methyl-2-pyrrolidinyl)methoxy]phenyl]-3-(4-methylphenyl)-2-propenamide

Following the procedure of Example 143(c)-(d), except substituting 3-(4-methylphenyl)-2-propenoic acid for 3-(3,4-dichlorophenyl)-2-propenoic acid, afforded the title compound.

Biological Data:

CCR5 Receptor Binding Assay CHO cell membranes (0.25×10^6 cell equivalents) derived from CHO cells stably transfected with CCR5 were incubated with 0.3 ^{125}I-RANTES in a 96 well plate for 45 min at room temperature (final reaction volume 200 ul). The reaction was terminated by filtration and the filters (GF/C) were washed twelve times with a solution of phosphate buffered saline containing 0.1 % bovine serum albumin and 0.05 % NaN_3. The radioactivity bound to filters was measured by liquid scintillation spectrometry. Non-specific binding was determined

in the presence of unlabelled RANTES (10 or 30 nM) and averages 30-50% of total binding.

CCR5 Receptor Functional Assay

The cellular functional assay used to assess antagonist activity of compounds was RANTES-induced Ca^{2+} mobilization in RBL 2H3 cells stably expressing the hCCR5 receptor (RBL 2H3 hCCR5). Agonist activity is determined by Ca^{2+} mobilization in the same cells which is inhibitable by a selective CCR5 antagonist. Cells were grown to 80-100% confluency in T-150 flasks and washed with phosphate-buffered saline. Cells were lifted from the flasks by treating with 3 mL of 1 mM EDTA for 3 min at room temperature and diluting to 2 X 10^6 cells/mL with Krebs Ringer Henseleit buffer (KRH; 118 mM NaCl, 4.6 mM KCl, 25 mM $NaHCO_3$, 1 mM KH_2PO_4 and 11 mM glucose) containing 5 mM HEPES (pH 7.4), 1 mM $CaCl_2$, 1 mM $MgCl_2$ and 0.1% BSA and centrifuged at 200g for 3 min. Cells were resuspended at 2 X 10^6 cells/mL in the same buffer with 2 μM Fura-2AM, and incubated for 35 min at 37° C. Cells were centrifuged at 200-x g for 3 min and resuspended in the same buffer without Fura-2AM, then incubated for 15 min at 37° C to complete the hydrolysis of intracellular Fura-2AM, and then centrifuged as before. Cells (10^6 cells/mL) were resuspended in cold KRH with 5 mM HEPES (pH 7.4), 1 mM $CaCl_2$, 1 mM $MgCl_2$ and 0.1% gelatin and maintained on ice until assayed. For antagonist studies, aliquots (2 mL) of cells were prewarmed at 37° C for 5 min in 3 mL plastic cuvettes and fluorescence measured in a fluorometer (Johnson Foundation Biomedical Group, Philadelphia, PA, USA) with magnetic stirring and temperature maintained at 37° C. Excitation was set at 340 nm and emission set at 510 nm. Various concentrations of antagonists or vehicle were added and fluorescence monitored for ~15 sec to ensure that there was no change in baseline fluorescence, followed by the addition of 33 nM RANTES. Maximal Ca^{2+} attained after 33 nM RANTES stimulation was calculated as described by Grynkiewicz *et al.*, (1985). The percent of maximal RANTES-induced Ca^{2+} was determined for each concentration of antagonist and the IC_{50}, defined as the concentration of test compound that inhibits 50% of the maximal 33 nM RANTES response, obtained from the concentration-response curves (5-7 concentrations of antagonists).

The compounds of this invention show CCR5 receptor modulator activity having IC_{50} values in the range of 0.0001 to 100 μM. The full structure/activity relationship has not yet been established for the compounds of this invention. However, given the disclosure herein, one of ordinary skill in the art can utilize the

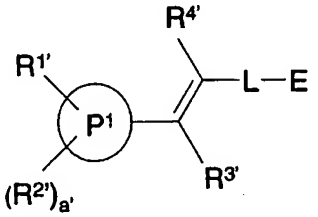
present assays in order to determine which compounds of formula (I) are modulators of the CCR5 receptor and which bind thereto with an IC_{50} value in the range of 0.0001 to 100 μM.

All publications, including, but not limited to, patents and patent applications cited in this specification, are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration it is believed that one skilled in the art can, given the preceding description, utilize the present invention to its fullest extent. Therefore any examples are to be construed as merely illustrative and not a limitation on the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is claimed is:

1. A method of treating a CCR5-mediated disease state in mammals which comprises administering to a mammal in need of such treatment, an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

the basic nitrogen in moiety E may be optionally quaternized with C_{1-6}alkyl or is optionally present as the N-oxide;

P^1 is phenyl, fused bicyclic aryl, a 5- to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulfur, or a fused bicyclic heterocyclic ring of 8 to 11 members containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulfur;

L is $CONR^{5'}$;

$R^{1'}$ and $R^{2'}$ are independently hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-7}cycloalkyl, C_{3-6}cycloalkenyl, $(CH_2)_b NR^{6'}R^{7'}$, $(CH_2)_b NR^{6'}COR^{8'}$, $(CH_2)_b NR^{6'}CO_2R^{9'}$, $(CH_2)_b NR^{6'}SO_2R^{10'}$, $(CH_2)_b CONR^{11'}R^{12'}$, hydroxy$C_{1-6}$alkyl, C_{1-4}alkoxyalkyl (optionally substituted by a C_{1-4}alkoxy or hydroxy group), $(CH_2)_b CO_2C_{1-6}$alkyl, $(CH_2)_c OC(O)R^{13'}$, $CR^{14'}{=}NOR^{15'}$, $CNR^{16'}{=}NOR^{15'}$, $COR^{17'}$, $CONR^{11'}R^{12'}$, $CONR^{11'}(CH_2)_d OC_{1-4}$alkyl, $CONR^{11'}(CH_2)_b CO_2R^{18'}$, $CONHNR^{19'}R^{20'}$, $CONR^{11'}SO_2R^{21'}$, $CO_2R^{22'}$, cyano, trifluoromethyl, $NR^{6'}R^{7'}$, $NR^{6'}COR^{8'}$, $NR^{23'}CO(CH_2)_b NR^{23'}R^{24'}$, $NR^{23'}CONR^{23'}R^{24'}$, $NR^{6'}CO_2R^{9'}$, $NR^{6'}SO_2R^{10'}$, $N{=}CNR^{23'}NR^{23'}R^{24'}$, nitro, hydroxy, C_{1-6}alkoxy, hydroxyC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-6}alkoxy, $OC(O)NR^{25'}R^{26'}$, $SR^{27'}$, $SOR^{28'}$, $SO_2R^{28'}$, $SO_2NR^{29'}R^{30'}$, halogen, C_{1-6}alkanoyl, $CO_2(CH_2)_b OR^{31'}$, or $R^{1'}$ is phenyl or $R^{1'}$ is a 5 to 7-membered heterocyclic ring containing 1 to 4 heteroatoms selected from oxygen, nitrogen or sulfur, which are optionally substituted by one or two of $R^{32'}$;

or $R^{1'}$ is an optionally substituted, fused carbocyclic ring of 5 to 7-members, which may be partly or wholly unsaturated, or $R^{1'}$ is an optionally substituted, fused

heterocyclic ring of 5 to 7-members containing 1 to 4 heteroatoms selected from nitrogen, oxygen, or sulfur, which may be partly or wholly unsaturated;

$R^{3'}$ is hydrogen or C_{1-6}alkyl;

$R^{4'}$ is hydrogen, C_{1-6}alkyl, C_{1-6}alkylCONH, or halogen;

$R^{5'}$ is hydrogen or C_{1-6}alkyl;

$R^{14'}$, $R^{15'}$, $R^{16'}$ $R^{17'}$, $R^{18'}$, $R^{19'}$ $R^{20'}$, $R^{23'}$, $R^{24'}$, $R^{27'}$, and $R^{31'}$ are independently hydrogen or C_{1-6}alkyl;

$R^{6'}$ and $R^{7'}$ are independently hydrogen or C_{1-6}alkyl, or $R^{6'}$ and $R^{7'}$ together with the nitrogen to which they are attached, forms a 5- to 6-membered heterocyclic ring, which may optionally be substituted by an oxo group, and, when there are six members, may optionally contain in the ring one oxygen or one sulfur atom;

$R^{8'}$ is hydrogen, C_{1-6}alkyl, or C_{1-4}alkoxyalkyl;

$R^{9'}$, $R^{21'}$, and $R^{28'}$ are independently C_{1-6}alkyl;

$R^{10'}$ is C_{1-6}alkyl or phenyl;

$R^{11'}$ and $R^{12'}$ are independently hydrogen or C_{1-6}alkyl, or $R^{11'}$ and $R^{12'}$ together with the nitrogen to which they are attached form a 5- to 6-membered saturated heterocyclic ring which, when there are 6 ring members, may optionally contain in the ring one oxygen or one sulfur atom;

$R^{13'}$ is C_{1-4}alkyl, optionally substituted by a C_{1-6}alkoxy;

$R^{22'}$ is hydrogen or C_{1-6}alkyl optionally substituted with one or two substituents selected from C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, or $NR^{6'}R^{7'}$;

$R^{25'}$ and $R^{26'}$ are independently hydrogen or C_{1-6}alkyl, or $R^{25'}$ and $R^{26'}$ together with the nitrogen to which they are attached form a 5- to 6-membered heterocyclic ring which, when there are six ring members, may optionally contain in the ring one oxygen or sulfur atom;

$R^{29'}$ and $R^{30'}$ are independently hydrogen or C_{1-6}alkyl, or $R^{29'}$ and $R^{30'}$ together with the nitrogen to which they are attached form 5- to 6-membered heterocyclic ring which, when there are six ring members, may optionally contain in the ring one oxygen or one sulfur atom;

$R^{32'}$ is hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{3-6}cycloalkenyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylOC_{1-6}alkyl, $CONR^{33'}R^{34'}$, $CO_2R^{35'}$, cyano, aryl, trifluoromethyl, $NR^{36'}R^{37'}$, nitro, hydroxy, C_{1-6}alkoxy, C_{1-6}alkanoyl, acyloxy, or halogen;

$R^{33'}$, $R^{34'}$, $R^{35'}$, $R^{36'}$, and $R^{37'}$ are independently hydrogen or C_{1-6}alkyl;

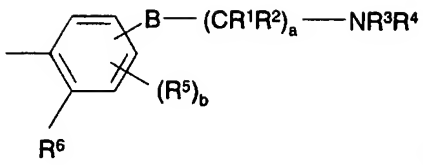
a' is 1, 2, or 3;

b' is 1, 2, 3 or 4;

c' is 0, 1, 2 or 3;

d' is 1, 2 or 3;

E represents (a):



(a);

in which

B is oxygen, $S(O)_c$, $CR^7{=}CR^8$, or CR^7R^8, or B is NR^9;

R^1 and R^2 are independently hydrogen or C_{1-6}alkyl; alternatively $B(CR^1R^2)_a$ is $OCR^1R^2CR^1(OH)CR^1R^2$ or $OCR^1R^2CR^1(OCOCH_3)CR^1R^2$;

R^3 and R^4 are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include C_{1-6}alkyl, aryl, $CONR^{10}R^{11}$, $NR^{10}R^{11}$, hydroxy, $OCOR^{12}$, $NHCOC_{0-6}$alkyl where alkyl is optionally substituted by OH, $NHCOCF_3$, $NHSO_2R^{13}$, and $NHCO_2R^{14}$;

R^5 is hydrogen, C_{1-6}alkyl, aryl, CN, $CONR^{15}R^{16}$, CO_2R^{17}, trifluoromethyl, $NHCO_2R^{18}$, hydroxy, C_{1-6}alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, OCF_3, $S(O)_dR^{19}$, $SO_2NR^{20}R^{21}$ or halogen;

R^6 is hydrogen, C_{1-6}alkyl, aryl, trifluoromethyl, hydroxy, C_{1-6}alkoxy or halogen, or R^6 taken together with $R^{5'}$ forms a group D where D is $(CR^{22}R^{23})_e$ or D is $(CR^{22}R^{23})_f$-G where G is oxygen, sulfur or $CR^{22}{=}CR^{23}$, $CR^{22}{=}N$, $=CR^{22}O$, $=CR^{22}S$, or $=CR^{22}{-}NR^{23}$;

R^7, R^8, R^{10}, R^{11}, R^{12}, R^{15}, R^{16}, R^{17}, R^{20}, R^{21}, R^{22}, and R^{23} are independently hydrogen or C_{1-6}alkyl;

R^9 is hydrogen, C_{1-6}alkyl, or phenylC_{1-6}alkyl;

R^{13}, R^{14}, R^{18}, and R^{19} are independently C_{1-6}alkyl;

a is 1, 2, 3, or 4;

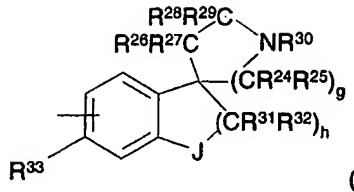
b is 1 or 2;

c and d are independently 0, 1 or 2;

e is 2, 3 or 4;

f is 0, 1, 2 or 3;

alternatively, E represents (b):



(b);

R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{31}, and R^{32} are independently hydrogen or C_{1-6}alkyl;

R^{30} is hydrogen, C_{1-6}alkyl, or C_{3-7}cycloalkyl;

R^{33} is hydrogen, C_{1-6}alkyl, trifluoromethyl, hydroxy or halogen, or R^{33} and $R^{5'}$ together form a group -K- where K is $(CR^{34}R^{35})_i$ or K is $(CR^{34}R^{35})_j$ -M and M is oxygen, sulfur, $CR^{34}=CR^{35}$, $CR^{34}=N$, or N=N;

J is oxygen, $CR^{36}R^{37}$, or NR^{38}, or J is a group $S(O)_k$;

R^{34}, R^{35}, R^{36}, R^{37}, and R^{38} are independently hydrogen or C_{1-6}alkyl;

g is 1, 2 or 3;

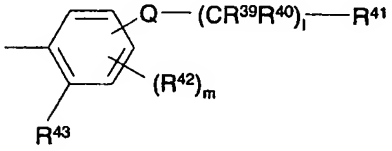
h is 1, 2 or 3;

i is 2, 3, or 4;

j is 0, 1, 2, or 3;

k is 0, 1 or 2;

alternatively, E represents (c):



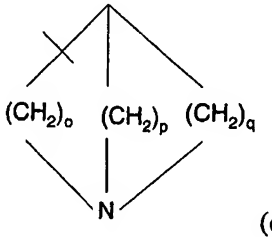
(c);

in which:

Q is oxygen, $S(O)_n$, $CR^{44}=CR^{45}$, $CR^{44}R^{45}$, or Q is NR^{46};

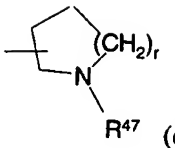
R^{39} and R^{40} are independently hydrogen or C_{1-6}alkyl;

R^{41} is a group of formula (d):



(d)

or R^{41} is a group of formula (e):



(e)

R^{42} is hydrogen, C_{1-6}alkyl, aryl, CN, $CONR^{48}R^{49}$, CO_2R^{50}, trifluoromethyl, $NHCO_2R^{51}$, hydroxy, C_{1-6}alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, OCF_3, $S(O)_sR^{52}$, $SO_2NR^{53}R^{54}$, or halogen;

R^{43} is hydrogen or R^{43} together with $R^{5'}$ forms a group R where R is $CR^{55}=CR^{56}$, $CR^{55}=CR^{56}CR^{55}R^{56}$, or $(CR^{55}R^{56})t$;

R^{44}, R^{45}, R^{46}, R^{48}, R^{49}, R^{50}, R^{53}, R^{54}, R^{55}, and R^{56} are independently hydrogen or C_{1-6}alkyl;

R^{47} is hydrogen, C_{1-6}alkyl, or C_{3-7} cycloalkyl;

R^{51} and R^{52} are independently C_{1-6}alkyl;

l is 0, 1, 2, or 3;

m is 1 or 2;

n is 0, 1, or 2

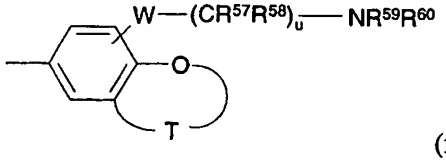
o, p, and q are independently integers having the value 1, 2, or 3;

r is 0,1, 2, or 3;

s is 0, 1, or 2;

t is 2 or 3;

alternatively, E represents (f):



(f);

R^{57} and R^{58} are independently hydrogen or C_{1-6}alkyl;

R^{59} and R^{60} are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include C_{1-6}alkyl, aryl, $CONR^{61}R^{62}$, $NR^{61}R^{62}$, hydroxy, $OCOR^{63}$, $NHCOC_{0-6}$alkyl where alkyl is optionally substituted by OH, $NHCOCF_3$, $NHSO_2R^{64}$, and $NHCO_2R^{65}$;

T is $-(CR^{66}R^{67})_v-$ or $-O(CR^{66}R^{67})_w-$;

W is oxygen, $S(O)_x$, NR^{68}, or W is $CR^{69}=CR^{70}$ or $CR^{69}R^{70}$;

R^{61}, R^{62}, R^{63}, R^{66}, R^{67} R^{68}, R^{69}, and R^{70} are independently hydrogen or C_{1-6}alkyl;

R^{64} and R^{65} are independently C_{1-6}alkyl;

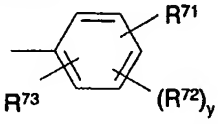
u is 1 to 4;

v is 2 or 3;

w is 1, 2, or 3;

x is 0, 1 or 2;

alternatively, E represents a group (g):



(g);

R^{71} is an optionally substituted 5 to 7-membered saturated or partially saturated heterocyclic ring containing 1 to 3 heteroatoms selected from nitrogen, oxygen or sulfur or R^{71} is an optionally substituted 6,6 or 6,5 bicyclic ring containing a nitrogen atom and optionally a further heteroatom selected from oxygen, nitrogen or sulfur;

R^{72} is hydrogen, C_{1-6}alkyl, aryl, CN, $CONR^{74}R^{75}$, CO_2R^{76}, trifluoromethyl, $NHCO_2R^{77}$, hydroxy, C_{1-6}alkoxy, benzyloxy, $OCH_2CO_2C_{1-6}$alkyl, OCF_3, $S(O)_zR^{78}$, $SO_2NR^{79}R^{80}$, or halogen;

R^{73} is hydrogen, C_{1-6}alkyl, hydroxy, C_{1-6}alkoxy or halogen, or R^{73} and $R^{5'}$ taken together from a group -X- where X is $(CR^{81}R^{82})_{aa}$ or X is $(CR^{81}R^{82})_{ab}$-Y and Y is oxygen, sulfur or $CR^{81}=CR^{82}$;

R^{74}, R^{75}, R^{76}, R^{79}, R^{80}, R^{81}, and R^{82} are independently hydrogen or C_{1-6}alkyl;

R^{77} and $R^{78}$are independently C_{1-6}alkyl;

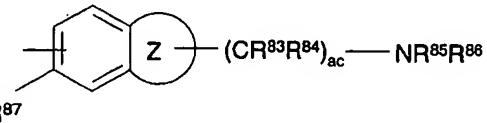
y is 1 or 2;

z is 0, 1, or 2;

aa is 2, 3 or 4;

ab is 0, 1, 2 or 3;

alternatively, E represents group (h):



(h);

R^{83} and R^{84} are independently hydrogen or C_{1-6}alkyl;

R^{85} and R^{86} are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally

substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include C_{1-6}alkyl, aryl, $CONR^{88}R^{89}$, $NR^{90}R^{91}$, hydroxy, $OCOR^{92}$, $NHCOC_{0-6}$alkyl where alkyl is optionally substituted by OH, $NHCOCF_3$, $NHSO_2R^{93}$, and $NHCO_2R^{94}$;

R^{87} is hydrogen or C_{1-6}alkyl, C_{1-6}alkoxy, or halogen, or R^{87} together with $R^{5'}$ forms a group -AA- where AA is $(CR^{95}R^{96})_{ad}$ or AA is $(CR^{95}=CR^{96})_{ae}$-AB and AB is oxygen, sulfur, $CR^{95}=CR^{96}$, $CR^{95}=N$, $CR^{95}NR^{96}$ or N=N;

Z is an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulfur;

R^{88}, R^{89}, R^{90}, R^{91}, R^{92}, R^{95}, and R^{96} are independently hydrogen or C_{1-6}alkyl;

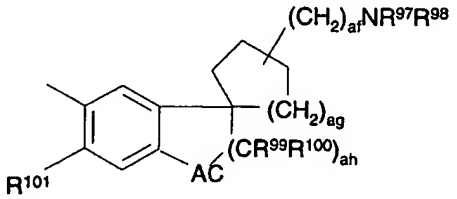
R^{93} and R^{94} are independently C_{1-6}alkyl;

ac is 0 to 4;

ad is 1, 2 or 3;

ae is 0, 1 or 2;

alternatively, E represents group (i):



(i);

R^{97} and R^{98} are independently hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aralkyl, or together with the nitrogen atom to which they are attached form an optionally substituted 5- to 7-membered heterocyclic ring which may contain an additional heteroatom selected from oxygen, nitrogen or sulfur, where optional substituents include C_{1-6}alkyl, aryl, $CONR^{102}R^{103}$, $NR^{104}R^{105}$, hydroxy, $OCOR^{106}$, $NHCOC_{0-6}$alkyl where alkyl is optionally substituted by OH, $NHCOCF_3$, $NHSO_2R^{107}$, and $NHCO_2R^{108}$;

R^{99} and R^{100} are independently hydrogen or C1-6alkyl;

R^{101} is hydrogen or C_{1-6}alkyl or R^{101} and $R^{5'}$ together form a group -AD- where AD is $(CR^{109}R^{110})$ai or AD is $(CR^{109}R^{110})_{aj}$-AE and AE is oxygen, sulfur or $CR^{109}=CR^{110}$;

AC is oxygen, $CR^{111}R^{112}$ or NR^{113} or AC is a group $S(O)_{ak}$;

R^{102}, R^{103}, R^{104}, R^{105}, R^{106}, R^{109}, R^{110}, R^{111}, R^{112}, and R^{113} are independently hydrogen or C_{1-6}alkyl;

R^{107} and R^{108} are independently C1-6alkyl;

af is 0, 1, 2, 3, or 4;

ag is 1, 2, or 3;

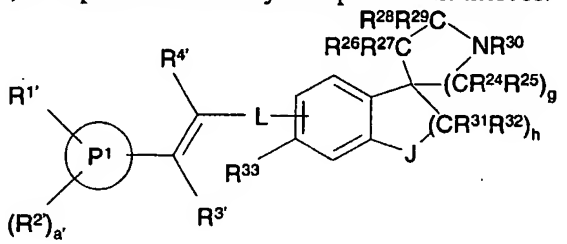
ah is 1, 2, 3 or 4;

ai is 2, 3 or 4;

aj is 0, 1, 2, or 3; and

ak is 0, 1 or 2.

2. The method of claim 1 wherein the compound of formula (I) is selected from a subgenus of formula (Ia) or a pharmaceutically acceptable salt thereof:



Formula (Ia)

wherein:

$R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, P^1, a', L, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{33}, J, g, and h are defined in claim 1.

3. The method as claimed in claim 1 wherein the compound is selected from:

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-phenyl-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3,4-dichlorophenyl)-2-propenamide;

N-[4-Methoxy-3-[(2S)-(1-methyl-2-pyrrolidinyl)methoxy]phenyl]-3-(4-methylphenyl)-2-propenamide;

N-[4-Methoxy-3-[(2S)-(1-methyl-2-pyrrolidinyl)methoxy]phenyl]-3-(3,4-dichlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(4-chlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3,4-difluorophenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2-naphthalenyl)-2-propenamide hydrochloride;

N-[3-[2-(2,2,6,6-Tetramethylpiperidin-1-yl)ethoxy]-4-methoxy-phenyl]-3-(3,4-dichlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3,4-dichlorophenyl)-2-propenamide;

N-[1-[2-[Bis(1-methylethyl)amino]ethyl]-1,2,3,4-tetrahydroquinol-7-yl]-3-(3,4-dichlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3-chlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3-chlorophenyl)-2-propenamide;

N-[3-[2-(cis-2,6-Dimethylpiperidin-1-yl)ethoxy]-4-methoxyphenyl]-3-(3-chlorophenyl)-2-propenamide;

N-[3-[2-(N-Cyclohexyl-N-isopropylamino)ethoxy]-4-methoxy-phenyl]-3-(3-chlorophenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(4-chlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(4-chlorophenyl)-2-propenamide;

N-[3-[2-(cis-2,6-Dimethylpiperidin-1-yl)ethoxy]-4-methoxyphenyl]-3-(4-chlorophenyl)-2-propenamide;

N-[3-[2-(N-Cyclohexyl-N-isopropylamino)ethoxy]-4-methoxy-phenyl]-3-(4-chlorophenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methylphenyl]-3-[(3,4-methylenedioxy)phenyl]-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-[(3,4-methylenedioxy)phenyl]-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-[(3,4-methylenedioxy)phenyl]-2-propenamide;

N-[3-[2-(N-Cyclohexyl-N-isopropylamino)ethoxy]-4-methoxy-phenyl]-3-[(3,4-methylenedioxy)phenyl]-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3,4-difluorophenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methylphenyl]-3-(3,4-difluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3,4-difluorophenyl)-2-propenamide;

N-[3-[2-(cis-2,6-Dimethylpiperidin-1-yl)ethoxy]-4-methoxyphenyl]-3-(3,4-difluorophenyl)-2-propenamide;

N-[3-[2-(N-Cyclohexyl-N-isopropylamino)ethoxy]-4-methoxy-phenyl]-3-(3,4-difluorophenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methylphenyl]-3-(2-naphthalenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(2-naphthalenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2-naphthalenyl)-2-propenamide;

N-[3-[2-(N-Cyclohexyl-N-isopropylamino)ethoxy]-4-methoxy-phenyl]-3-(2-naphthalenyl)-2-propenamide;

(E)-N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3-chlorophenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethyl]-2-oxo-(3H)-benzoxazol-5-yl]-3-(3,4-dichlorophenyl)-2-propenamide;

N-[4-[2-[Bis(1-methylethyl)amino]ethyl]-3,4-dihydro-3-oxo-2H-1,4-benzoxazin-6-yl]-3-(3,4-dichlorophenyl)-2-propenamide;

N-[4-[2-[Bis(1-methylethyl)amino]ethyl]-3,4-dihydro-2H-1,4-benzoxazin-6-yl]-3-(3,4-dichlorophenyhl-2-propenamide;

N-[2,3-Dihydro-1-[2-[bis(1-methylethyl)amino]ethyl]-1H-indol-6-yl]-3-(3,4-dichlorophenyl)-2-propenamide;

(E)-N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(5-indolyl)-2-propenamide;

(E)-N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl)-3-(6-indolyl)-2-propenamide;

(E)-•••-Dimethyl-N-[3-[2-[bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-phenyl-2-propenamide;

(Z)-N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl)-•-(acetylamino)-3-(3,4-dichlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3,4-dichlorophenyl)]-2-propenamide;

(E)-N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(5,6,7,8-tetrahydronaphth-2-yl)-2-propenamide trifluoroacetate salt;

N-(Spiro[benzofuran-3(2H),4'-piperidin]-5-yl)-3-(3,4-dichlorophenyl)-2-propenamide;

N-[1'-(Isopropyl)spiro[benzofuran-3(2H)4'-piperidin]-5-yl]-3-(3,4-dichlorophenyl)-2-propenamide;

(E)-N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(4-chloro-3-methylphenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxypheny]-3-(4-fluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-[4-(trifluoromethyl)phenyl]-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-[3-(trifluoromethyl)phenyl]-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-[3-(trifluoromethyl)phenyl]-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-[3-(trifluoromethyl)phenyl]-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2-chlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(2-chlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2-chlorophenyl)]-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2,4-dichlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(2,4-dichlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2,4-dichlorophenyl)]-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2,6-dichlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(2,6-dichlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2,6-dichlorophenyl)]-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3,5-difluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3,5-difluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3,5-difluorophenyl)]-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2,5-difluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(2,5-difluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2,5-difluorophenyl)]-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2,4-difluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(2,4-difluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2,4-difluorophenyl)]-2-propenamide(SB-383258);

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3-fluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3-fluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3-fluorophenyl)]-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2-chloro-6-fluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(2-chloro-6-fluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2-chloro-6-fluorophenyl)]-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(4-bromo-2-fluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(4-bromo-2-fluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(4-bromo-2-fluorophenyl)]-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(4-chloro-2-fluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(4-chloro-2-fluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(4-chloro-2-fluorophenyl)]-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2-chloro-4-fluorophenyl)-2-propenamide

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(2-chloro-4-fluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2-chloro-4-fluorophenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2,6-difluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(2,6-difluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2,6-difluorophenyl)]-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(4-bromophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(4-bromophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(4-bromophenyl)]-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(4-chloro-3-nitrophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(4-chloro-3-nitrophenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-[4-(1-methylethyl)phenyl]-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-[4-(1-methylethyl)phenyl]-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-[4-(1-methylethyl)phenyl]-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(5-bromo-2-methoxyphenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(5-bromo-2-methoxyphenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-([1,1'-biphenyl]-4-yl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-([1,1'-biphenyl]-4-yl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2,3-dihydro-1H-inden-5-yl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3-bromo-4-fluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3-bromo-4-fluorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3-bromo-4-fluorophenyl)]-2-propenamide;

(E)-N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3,5-dichlorophenyl)-2-propenamide trifluoroacetate;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3,5-dichlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3,5-dichlorophenyl)]-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3,4-dimethylphenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3,4-dimethylphenyl)-2-propenamide

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3,4-dimethylphenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(4-cyanophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(4-cyanophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(4-cyanophenyl)]-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-2-fluoro-3-phenyl-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-2-fluoro-3-phenyl-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-2-fluoro-3-phenyl-2-propenamide;

(E)-N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-[4-chloro-3-(trifluoromethyl)phenyl]-2-propenamide;

(E)-N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3,4-dichlorophenyl)-•-methyl-2-propenamide;

(E)-N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-[4-(trifluoromethyl)phenyl]-2-propenamide;

N-[3-[2-Acetoxy-3-[bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3,4-dichlorophenyl)-2-propenamide;

N-[3-[2-(4-Hydroxy-2,2,6,6-tetramethylpiperidin-1-yl)ethoxy]-4-methoxyphenyl]-3-(3,4-dichlorophenyl)-2-propenamide;

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H)4'-piperidin]-5-yl]-3-(3,5-dichlorophenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3-thienyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3-thienyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(3-thienyl)-2-propenamide;

N-[3-[2-(cis-2,6-Dimethylpiperidin-1-yl)ethoxy]-4-methoxyphenyl]-3-(3-thienyl)-2-propenamide;

N-[3-[2-(N-Cyclohexyl-N-isopropylamino)ethoxy]-4-methoxyphenyl]-3-(3-thienyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methylphenyl]-3-(4-pyridinyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(4-pyridinyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3-furanyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methylphenyl]-3-(3-furanyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3-furanyl)-2-propenamide;

N-[3-[2-(cis-2,6-Dimethylpiperidin-1-yl)ethoxy]-4-methoxyphenyl]-3-(3-furanyl)-2-propenamide;

N-[3-[2-(N-Cyclohexyl-N-isopropylamino)ethoxy]-4-methoxyphenyl]-3-(3-furanyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(2-thienyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propoxy]-4-methoxyphenyl]-3-(2-thienyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2-furanyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(1H-indol-3-yl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(1H-indol-2-yl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(1-methyl-1H-indol-2-yl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(benzo[b]thien-3-yl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2-benzofuranyl)-2-propenamide; and

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(benzo[b]thien-2-yl)-2-propenamide.

4. The method of claim 1 wherein the CCR5-mediated disease state is selected from COPD, asthma and atopic disorders, rheumatoid arthritis, atherosclerosis, sarcoidosis and other fibrotic disease, psoriasis, autoimmune diseases such as multiple sclerosis, inflammatory bowel disease, and HIV.

5. A compound of formula (I) selected from:

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(3,4-dichlorophenyl)-2-propenamide;

N-[3-[2-[Bis(1-methylethyl)amino]ethoxy]-4-methoxyphenyl]-3-(2-naphthalenyl)-2-propenamide hydrochloride;

N-[3-[2-(2,2,6,6-Tetramethylpiperidin-1-yl)ethoxy]-4-methoxy-phenyl]-3-(3,4-dichlorophenyl)-2-propenamide;

N-[3-[3-[Bis(1-methylethyl)amino]propyl]-4-methoxyphenyl]-3-(3,4-dichlorophenyl)-2-propenamide;

N-[3-[2-(4-Hydroxy-2,2,6,6-tetramethylpiperidin-1-yl)ethoxy]-4-methoxyphenyl]-3-(3,4-dichlorophenyl)-2-propenamide; and

N-[1'-(1-Methylethyl)spiro[benzofuran-3(2H)4'-piperidin]-5-yl]-3-(3,5-dichlorophenyl)-2-propenamide.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/17117

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/278, 311, 331, 357, 375, 408, 409, 415, 438, 443, 169, 471, 649, 657; 546/17, 232; 564/337, 428

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS--structure
DIALOG--multidata base, CCR5 chemokine

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P	CASDATA, CA abstract no. 131:87834, TAKEDA CHEMICAL INDUSTRIES, LTD. 'Preparation of benzoxepinecarboxamines, benzocycloheptenecarboxamides, naphthalenecarboxamines, and related compounds as CCR5 antagonists', abstract, WO 99/32100 A2 01 July 1999, see whole abstract and RN 229006-78-4.	1, 3, 4
X, P	CASDATA, CA abstract no. 130:311815, YAMANOUCHI PHARMACEUTICAL CO., LTD. 'Preparation of pyrazole derivatives as calcium-release dependent calcium channel inhibitors and inhibitors of interleukin-2 (IL-2) production', abstract, WO 99/19303 A1 22 April 1999, see whole abstract and RN223499-50-1.	1, 3, 4

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 03 NOVEMBER 1999	Date of mailing of the international search report 19 NOV 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer CELIA CHANG Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/17117

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CASDATA, CA abstract no. 73:76840, IMPERIAL CHEMICAL INDUSTRIES LTD. 'Alkanolamine derivatives with .beta.-adrenergic blocking activity', abstract, ZA 68/05360 A, 1968, see whole abstract and RN 28036-66-0 for treatment of asthma.	1, 3, 4
Y	CASDATA, CA abstract no. 90:87093, LABORATORIA MARTIN CUATRECASAS S.A. 'Cinnamanilides of pharmacological interest', abstract, ES 464943 A1, 01 September 1978, see whole abstract.	1, 3, 4
Y	KRAPCHO et al. Immunosuppressive activity of dimethyl aminopropyl thiocinnamanilide and related compounds. J. Med. Chem. January 1969, Vol. 12, pages 164-166, see Tables I-III.	1, 3, 4
Y	CASDATA, CA abstract no. 124:172731, DE VRIES, J.E. 'Immunosuppresive and anti-inflammatory properties of interleukin 10', abstract, Ann. Med. 1995, Vol. 27, No. 5, pages 537-541, see whole abstract.	1, 3, 4
Y	CASDATA, CA abstract no. 117:63005, NATIONAL HEART AND LUNG INSTITUTE, 'Immunosuppressants for treatment of lung diseases', abstract, WO 92/08474 A2, 29 May 1992, see whole abstract.	1, 3, 4
A	US 5,373,019 A (ZILCH ET AL.) 13 December 1994, see spiroindolines at columns 18-21 for treating fibrotic diseases.	2
A	Chem. abstr. Vol. 55, No. 23, 13 November 1961 (Columbus, OH, USA) page 689, column 2, abstract No. 24660f, GEORGE et al. 'Condensation of malono-*o*, *m*, and *p*-chloroanilic acids with aldehydes. V. With vanillin and piperonal', abstract, Agra. Univ. J. Res. 9, pt. 1, 15-19, (1960). See RN 131239-53-7 and 131239-54-8.	5
A	CASDATA, CA abstract no. 118:147852, Hall et al. 'The synthesis of pyrido[4,3-b]carbazoles from diphenylamine derivatives: alternative routes to and relay syntheses of ellipticines and olivacines', abstract, J. Chem. Soc. Perkin Trans. 1, 1992, Vol. 24, pages 3439-3450, see RN 146308-27-2.	5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/17117

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☒ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/17117

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A61K 31/34, 31/38, 31/40, 31/42, 31/44, 31/47, 31/135, 31/405; C07C 211/00; C07D 211/06, 491/107

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

514/278, 311, 331, 357, 375, 408, 409, 415, 438, 443, 169, 471, 649, 657; 546/17, 232; 564/337, 428

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1, annex B, part 1, section(f), Markush practice(v). In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1, 3-4, drawn to method of treating CCR5-mediated disease employing compounds wherein E=(a).
Group II, claims 1-4, drawn to method of treating CCR5-mediated disease employing compounds wherein E=(b).
Group III, claims 1, 3-4, drawn to method of treating CCR5-mediated disease employing compounds wherein E=(c).
Group IV, claims 1, 3-4, drawn to method of treating CCR5-mediated disease employing compounds wherein E=(d).
Group V, claims 1, 3-4, drawn to method of treating CCR5-mediated disease employing compounds wherein E=(e).
Group VI, claims 1, 3-4, drawn to method of treating CCR5-mediated disease employing compounds wherein E=(f).
Group VII, claims 1, 3-4, drawn to method of treating CCR5-mediated disease employing compounds wherein E=(g).
Group VIII, claims 1, 3-4, drawn to method of treating CCR5-mediated disease employing compounds wherein E=(h).
Group IX, claims 1, 3-4, drawn to method of treating CCR5-mediated disease employing compounds wherein E=(i).
Group X, claim 5, drawn to substituted cinnamanilides.

The inventions listed as Groups I-X do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, annex B, part 1, section(f)(v) they lack the same or corresponding special technical features for the following reasons: under annex B, part 1, section (f)(v) it was stated that when dealing with "alternatives" of elements in a compound claim, if it can be shown that at least one member of the alternative variation is not novel over the prior art an objection of lack of unity may be raised.

In the instant case, it was found that at least one member of the alternative variation wherein the claims are drawn to treating allergic disease i.e. asthma (see cinnamanilides are antiallergenic CA 90), employing a cinnamanilide of the claims (see compounds anticipating claim 1, E=(a), CA 70), is disclosed in the prior art, thus, not novel. Therefore, the method of treating a species of a disease mediated by CCR5 employing a specific groups of compound containing formula E=(a) to E=(i) lack the special technical feature linking them as to form a general inventive concept.